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Effects of 5-HT_3, D_1 and D_2 Receptor Antagonists on Ethanol- and Cocaine-Induced Locomotion

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LÊ, A. D. D. M. TOMKINS, G. HIGGINS, B. QUAN, E. M. SELLERS. *Effects of 5-HT_3, D_1 and D_2 dopamine receptor antagonists on ethanol and cocaine-induced locomotion.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 325–332, 1997.—The effects of acute treatment with 5-HT_3 receptor antagonists, ondansetron and ICS 205-930, on the stimulation of activity induced by ethanol- and cocaine were examined. Ethanol (1.8 or 2 g/kg i.p.) or cocaine (15 mg/kg i.p.) produced a significant increase in locomotor activity (LMA) in DBA/2N mice. Pretreatment with ondansetron or ICS 205-930, in doses ranging from 0.001 to 0.1 mg/kg (s.c), did not modify ethanol or cocaine induced stimulation of activity. In contrast, pretreatment with a 10 μg/kg dose of either SCH 23390 or spiperone, a D_1 and D_2 dopamine (DA) receptor antagonist respectively, completely antagonized the stimulation of LMA induced by ethanol. Similar dose of SCH23390, but not spiperone, blocked the stimulation of activity induced by cocaine. These results indicate that D_1 but not D 2 DA receptors play a significant role in cocaine induced hyperactivity whereas both D_1 and D 2 are involved the locomotor activating effects of ethanol.

Ethanol Cocaine Dopamine $5HT_3$ receptor Locomotor activity

A MODULATORY role in the activity of the mesolimbic dopamine (DA) system played by 5-HT_3 receptors has been demonstrated using a variety of approaches. Thus activation of 5-HT_3 receptor sites following the administration of the selective agonists, 2-methylserotonin (4) and l-phenylbiguanide (21), have been shown to facilitate DA release within the nucleus accumbens (NAcc). While, the selective 5-HT_3 antagonists themselves do not attenuate basal release of DA in this terminal region, DA release elicited by some psychoactive agents is attenuated by these compounds (2, 45, 46). For example, morphine, ethanol, and nicotine stimulated DA release have all been shown to be reversed following 5-HT_3 receptor blockade, while that elicited by the peripheral administration of amphetamine is not (2,45,46). Since the mesolimbic DA system has been implicated in modulating the reinforcing efficacy of many of these psychoactive drugs (2,3,9,18,34,43), the ability of the 5-HT_3 antagonists to attenuate behavioural indices of drug reinforcement has also been evaluated. Conditioned place preference is one paradigm which has been utilised for this purpose. Both morphine and nicotine induced place preference are blocked by the administration of the selective antagonists, ondansetron and MDL72222, but place preference elicited by amphetamine is not (3,14). While these data suggest that 5-HT_3 receptor antagonism may attenuate behaviours in other animal models of reinforcement, in particular, self-administration behaviour, this has not been substantiated, at least with respect to heroin and nicotine self-administration (6,16).

In contrast, there are numerous reports demonstrating that the voluntary consumption of ethanol can be attenuated by a range of 5-HT_3 antagonists (7,15,20,41), an effect which is reproducible across species, (e.g. mice, rats, marmosets and in alcohol abusing individuals; 17,20,35,41). In addition, the discriminative stimulus effects of ethanol are also blocked by 5-HT_3 antagonists (13), further implicating 5-HT 3 receptor activation in some of ethanol's behavioural effects. Since ethanol can enhance the firing of DA-ergic neurons in the ventral tegmental area (11,12) and increase dopamine (DA) release

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in the nucleus accumbens (8, 43, 46) it has been proposed that the rewarding effects of ethanol are mediated in part via its effects on mesolimbic DA function. As these neurochemical effects of ethanol on the DA system are susceptible to reversal following 5-HT_3 receptor blockade it has been suggested that this is the mechanism underlying 5-HT_3 mediated suppression of ethanol self-administration.

The mesolimbic dopamine system has also been implicated in playing a critical role in the hyperactivity elicited by various drugs of abuse (1, 8). Since it has been demonstrated that doses of ethanol which enhance locomotor activity, also increase DA release in the NAcc (18) and that 5-HT_3 receptor blockade has been shown to reduce ethanol-induced DA release (45, 46), it is conceivable that 5-HT_3 receptor antagonists should also suppress ethanol-induced hyperactivity. While this has not been examined directly, one experiment designed to examine the effects of ethanol on target and contextual learning, reported that MDL72222 attenuated ethanol-induced hyperactivity in their paradigm (27). The present study was designed to specifically examine the effects of the selective 5-HT_3 receptor antagonists, ICS205 930 and ondansetron, on ethanol stimulated locomotor activity in DBA/2N mice. The DBA/2N mouse strain was selected for these studies because ethanol has been shown to produce a pronounced hyperactivity response in this strain (8, 19, 40). As the rationale for this experiment is based on the hypothesis that ethanol-induced hyperactivity is mediated by the facilitation of DA activity, we also examined the effect of administration of D_1 and D_2 receptors antagonists on ethanol stimulated locomotor activity for comparative purposes. Finally, ICS205-930 has been shown by Reith (28) to attenuate cocaine-induced locomotor activity. In order to determine if the hyperactivity elicited by cocaine can also be modified by pharmacological manipulations in a similar manner to that elicited by ethanol, the effect of 5-HT_3, D_1 and D_2 receptor blockade was also evaluated.

MATERIALS AND METHODS

Animals and Housing

Male DBA/2N mice weighing approximately 22 gm were purchased from Charles River Canada Inc (Quebec). They were housed in group of 5 in plastic cages with food and water available ad libitum. The housing room was maintained at an ambient temperature of 21 q 1 C and kept on a 12 h light/dark cycle (lights on at 07:00).

Apparatus and Testing

The activity boxes were made from stainless steel with a dimensions of 9.6 × 5 × 4" (L × W × H). Two infrared photocells were mounted 0.5" above the wire mesh floor in such a manner that it divides the cage into 3 equal compartments, via which locomotor activity was automatically recorded.

Prior to testing, mice were habituated to the activity box for 6 sessions of 45 min each. In the last 3 habituating sessions, mice were injected with saline (10 ml/kg) prior to being placed in the activity boxes to familiarise them with the injection procedure. To determine the effect of ethanol on locomotor activity, mice were injected with a dose of 1.8 (ICS205 930 study) or 2.0 g/kg (ondansetron study) given as 16% w/v ethanol solution in saline. (We have found that the optimal dose of ethanol to produce activation of LMA varies from batch to batch of mice. For this reason, a pilot study was conducted in a separate group of mice (n = 12) from each batch to determine the appropriate test dose of ethanol for each experiment). Following ethanol administration, the mice were placed immediately into individual activity boxes and their activities were measured in 3 min blocks for a total period of 45 min.

Study 1. Effects of the 5-HT_3 Antagonist, ICS205-930, on Ethanol- and Cocaine-Induced Hyperactivity

Based on their baseline locomotor activity during the final days of habituation, the mice were divided into 5 groups (n = 12 each) in a stratified manner such that all groups had similar mean baseline activity score. Mice in groups 1 and 2 received a pretreatment of saline (sc), while those from groups 3, 4 and 5 received pretreatments of 0.001, 0.01 and 0.1 mg/kg of ICS 205-930 respectively. Thirty min later, ethanol was administered (1.8 g/kg) to all groups except group 1 which recieved a saline injection of similar volume. Immediately after the second injection, the mice were placed in the activity cages for 45 mins.

One week after the completion of the ethanol study, the mice were rehabituated to the activity boxes for 45 min per day for a period of three days. They were then reallocated to one of 5 groups (n = 12 per group) based on their activity and previous drug exposure. Mice in groups 1 and 2 received a pretreatment of saline (sc), while those from groups 3, 4 and 5 received pretreatments of 0.001, 0.01 and 0.1 mg/kg of ICS 205-930 respectively. Thirty minutes later, cocaine (15 mg/kg) was administered i.p. to all groups except group 1 which received a second saline injection.

Study 2. Effects of the 5-HT_3 Antagonist, Ondansetron, on Ethanol and Cocaine-Induced Hyperactivity

A separate group of male DBA/2N were habituated to the test apparatus and injection procedures. The design for these experiments were essentially similar to that described for ICS 205-930 above with the exception that the ethanol dose employed was 2 g/kg. The dose of cocaine was maintained the same. The doses of ondansetron examined were 0.01, 0.1 and 1 mg/kg.

Study 3. Effects of D_1 and D_2 Receptor Antagonists, SCH23390 and Spiperone on Ethanol and Cocaine-Induced Locomotor Activity

Sixty DBA/2N mice were employed for this study. Following 3 habituation sessions to the activity boxes, they were divided into 6 groups (n = 10 per group) based on their baseline locomotor activity as described in study 1. Mice from groups 1 and 2 were pretreated with saline (0.1ml/10g of body weight), those from groups 3 and 4 received pretreatment with 10 g/kg (sc) of the D_1 antagonist SCH23390, mice from the remaining groups (5 and 6) received pretreatment with the 10 g/kg (sc) of the D_2 antagonist, spiperone. Thirty minutes later mice from groups 2, 4 and 6 received a 1.8 g/kg dose of ethanol administered i.p., while those from groups 1, 3 and 5 received an equivalent volume of saline. Immediately following the latter injection, the mice were placed in indiviual locomotor activity cages and their activity monitored for 45 mins.

To examine the effects of the D_1 and D_2 antgonists on cocaine-induced hyperactivity, the mice were rehabituated to the activity boxes for 3 sessions of 45 min over a three day period. They were then reallocated to one of 6 groups and the effects of D_1 and D_2 antagonist on cocaine (15mg/kg, given by ip route) induced hyperactivity were examined in a similar manner as that described for ethanol.

Drugs

Ondansetron (Glaxo) and ICS 205-930 (Sandoz) were dissolved in saline and administered subcutaneously in a volume of 0.1 ml/10 gm. Spiperone and SCH 23390 (Research Biochemical Internationals) were disolved in saline and administered in the same volume as that of ondansetron or ICS 205-930.

Data Analysis

Although the LMAs were recorded with a 3 min block over a period of 45 min, preliminary inspection of the data reveals no differences in the pattern of drug effects on the time course of ethanol or cocaine action. For this reason, the total activity over the 45 min period for each of the experimental group were employed for data analyses and graphical presentation.

One-way analysis of variance was used to evaluate the effects of ondansetron and ICS205-930 on ethanol and cocaine induced hyperactivity. Two-way analysis of variance was employed to analyse the effects of spiperone and SCH23390 on ethanol and cocaine induced hyperactivity. Newman Keul' tests were used for post-hoc test where appropriate. The statistical significant level was set at 0.05.

RESULTS

Study 1. Effects of the 5-HT_3 Antagonist, ICS205-930, on Ethanol and Cocaine-Induced Hyperactivity

The effect of ICS205 930 on ethanol-induced hyperactivity in DBA/2N mice is shown in Fig, 1A. Analysis of variance ($F = 4.2$, df = 4,55, $p < 0.05$) revealed an overall drug effect. Post-hoc tests revealed that this was due to a marked increase in locomotor activity in ethanol-treated mice compared to saline treated controls. However, pretreatment with ICS205 930 did not significantly reverse the effect of ethanol at any dose examined.

Figure 1B shows the effect of ICS205-930 pretreatment on cocaine induced stimulation of locomotor activity. While analysis of variance revealed a significant difference between the groups, Newman-Keuls post hoc tests indicated that this was due to the increase in activity scores in all groups receiving cocaine. None of the doses of ICS205-930 examined significantly attenuated cocaine-induced hyperactivity when compared to the group of mice that were pretreated with saline prior to cocaine injection. These results indicate that ICS 205-930 did not modify the stimulation of activity induced by either ethanol or cocaine.

Study 2. Effects of the 5-HT_3 Antagonist, Ondansetron, on Ethanol and Cocaine-Induced Hyperactivity.

The effects of pretreatment with various doses of ondansetron on ethanol (panel a) and cocaine (panel b) induced hyperactivity are shown in Fig, 2. Analyses of variance followed by post-hoc tests revealed that administration of either ethanol ($F = 13.4$, df = 4,55, $p < 0.001$) or cocaine ($F = 12.9$, df = 4,55, $p < 0.001$) significantly enhanced locomotor activity. Pretreatment with various doses of ondansetron, however, did not modify the stimulation of activity induced by either of these drugs.

Study 3. Effects of D_1 and D_2 Receptor Antagonists, SCH23390 and Spiperone on Ethanol and Cocaine-Induced Locomotor Activity

The effects of SCH23390 and spiperone on locomotor activation induced by ethanol (panel a) and cocaine (panel b) are shown in Fig, 3. Analysis of variance ($F = 3.8$, df = 5,54, $p < 0.004$) followed by Newman Keuls post-hoc tests revealed that the activity scores of mice pretreated with SCH23390 or spiperone prior to ethanol treatment were significantly lower ($P < 0.05$) than the activity scores of mice pretreated with saline prior to ethanol. The doses of SCH23390 or spiperone employed did not affect locomotor activity by themselves since the activity scores for the SCH23390/saline or spiperone/saline groups were not significantly different ($p > 0.05$) from those of the saline/saline treated group.

Similar analyses ($F = 5.8$, df = 1,54, $p < 0.001$) also showed that there was a significant pretreatment effect on cocaine-induced hyperactivity. In saline pretreated mice, administration of cocaine produced a significant increase in activity as compare to saline alone treated mice ($p < 0.05$). The LMA of spiperone/cocaine treated mice was not significantly different from that of the saline/cocaine treated mice indicating that spiperone did not antagonize the stimualtion of activity induced by cocaine. SCH23390 completely antagonised the stimulation of LMA induced by cocaine as the LMA of the SCH23390/cocaine treated group were significantly lower than those of the saline/cocaine treated group and not different ($p > 0.05$) from those of saline/saline or SCH23390/saline treated group. There are no significant differences in the LMA of the saline/saline, spiperone /saline and SCH23390/saline ($p > 0.05$) which indicates that spiperone or SCH 23390 did not affect LMA by itself.

DISCUSSION

The results of the present study show that administration of either ethanol or cocaine elicits a marked enhancement in locomotor activity behaviour in the DBA/2N mouse strain. While ethanol-induced hyperactivity is not reliably produced in rats (23, 26), our findings with ethanol in this mouse strain are consistent with previous reports (8,40). Selective blockade of D_1 or D_2 receptors by the administration of either SCH23390 or spiperone respectively, reversed ethanol's effects on locomotor activity. Since neither of these drugs administered alone altered baseline activity, the effects on ethanol-induced hyperactivity appear to be specific. However, under the same experimental conditions ethanol-induced hyperactivity was not attenuated by the 5-HT_3 receptor antagonists, ICS205-930 and ondansetron. Similar results were obtained in the cocaine-induced hyperactivity studies. Thus, the effects of cocaine were reversed by direct pharmacological manipulations of the DA system, but not by the administration of the 5-HT_3 receptor antagonists.

These results further demonstrate that ethanol-induced hyperactivity is dependent on DA transmission since blockade of either the D_1 or D_2 receptor subtype completely reversed ethanol's effects. These data are in agreement with those of Risinger et al (30) who also demonstrated suppression of ethanol-induced behavioural activation following the administration of the DA antagonist, haloperidol. Since the antagonists used were administered peripherally, the neuroanatomical sites associated with the dopaminergic system involved in mediating these effects of ethanol can not be directly inferred. However, a number of studies have shown that ethanol administration stimulates the release of dopamine in the NAcc and striatum (2,11,45,46). Furthermore, Imperato and Di Chiara (18) have shown that low doses of ethanol which produced behavioural activation in rats, selectively facilitated dopamine release in the NAcc, while high doses also enhance DA release in the striatum. Therefore, it seems reasonable to propose

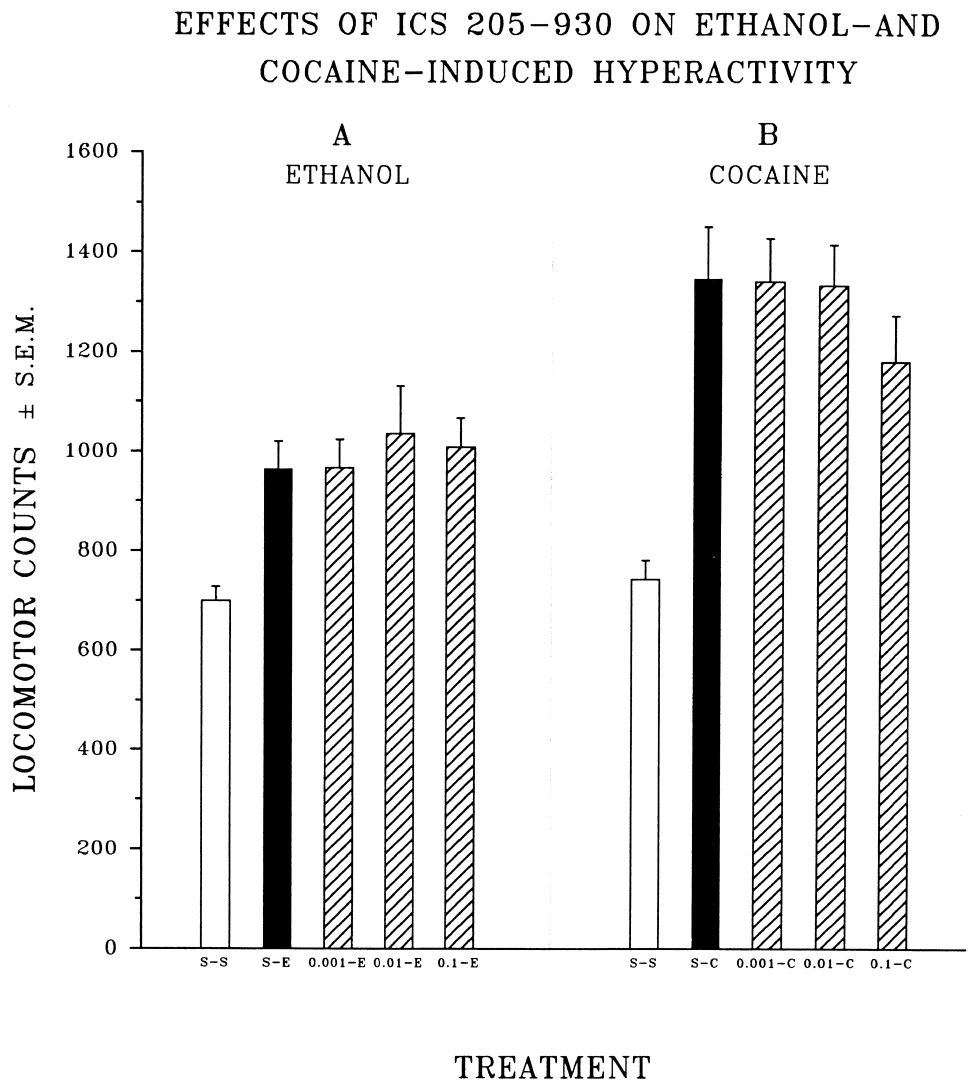

FIG. 1. Effects of pretreatment with various doses of ICS205-930 on ethanol- (panel a) and cocaine- (panel b) induced hyperactivity in DBA/2N mice. $N = 12$ mice per group. The numbers below the bars reflect doses in mg/kg; S: saline and E: ethanol. Vertical lines reflect positive half of the S.E.M.

that activation of mesolimbic DA function by ethanol may underlie its behavioural activating properties.

Since 5-HT_3 receptor antagonists have been shown to modify a number of behavioural and neurochemical effects of ethanol, the rationale for investigating their ability to reverse the locomotor activating effects of ethanol seemed well grounded (2,7,20,41,45,46). The failure to observe any effects of 5-HT_3 receptor antagonists on ethanol induced locomotion in the present study is rather difficult to explain in light of these findings, as well as the observation that DA antagonist can reduce the stimulation of locomotor activity by ethanol. One possible explanation is that although DA in the NAcc does play an important role in ethanol induced hyperactivity, the relationship between the amount of DA release and the hyperactivity induced is not linear. For example, in rats, a variety of studies mentioned above have shown that ethanol can stimulate the release of DA in the NAcc and striatum, however, hyperactivity induced by low doses of ethanol has proven difficult to demonstrate in this species (23, 26). In addition, unlike the classic psychomotor stimulants, ethanol-induced hyperactivity may be mediated via modulation of several neurotransmitter systems (19,25,30) rather than throug modification of DA-ergic activity alone. It is therefore possible that an involvement of the DA system in the stimulation of locomotor activity elicited by ethanol is demonstrable only when mesolimbic DA activity is completely antagonized.

Another 5-HT_3 receptor antagonist, MDL72222, has been reported to attenuate ethanol-induced hyperactivity in rats (27). While these data are inconsistent with those reported here, these differences may be due to several factors. Besides the differences in species and sex employed, MDL72222 but not ondansetron and ICS205-930, has been shown to modify ethanol kinetics (13) and therefore the possibility that the attenuation of ethanol-hyperactivity by MDL72222 might be mediated through an alteration in blood alcohol levels can not be ruled out. Moreover, LMA induced by ethanol was

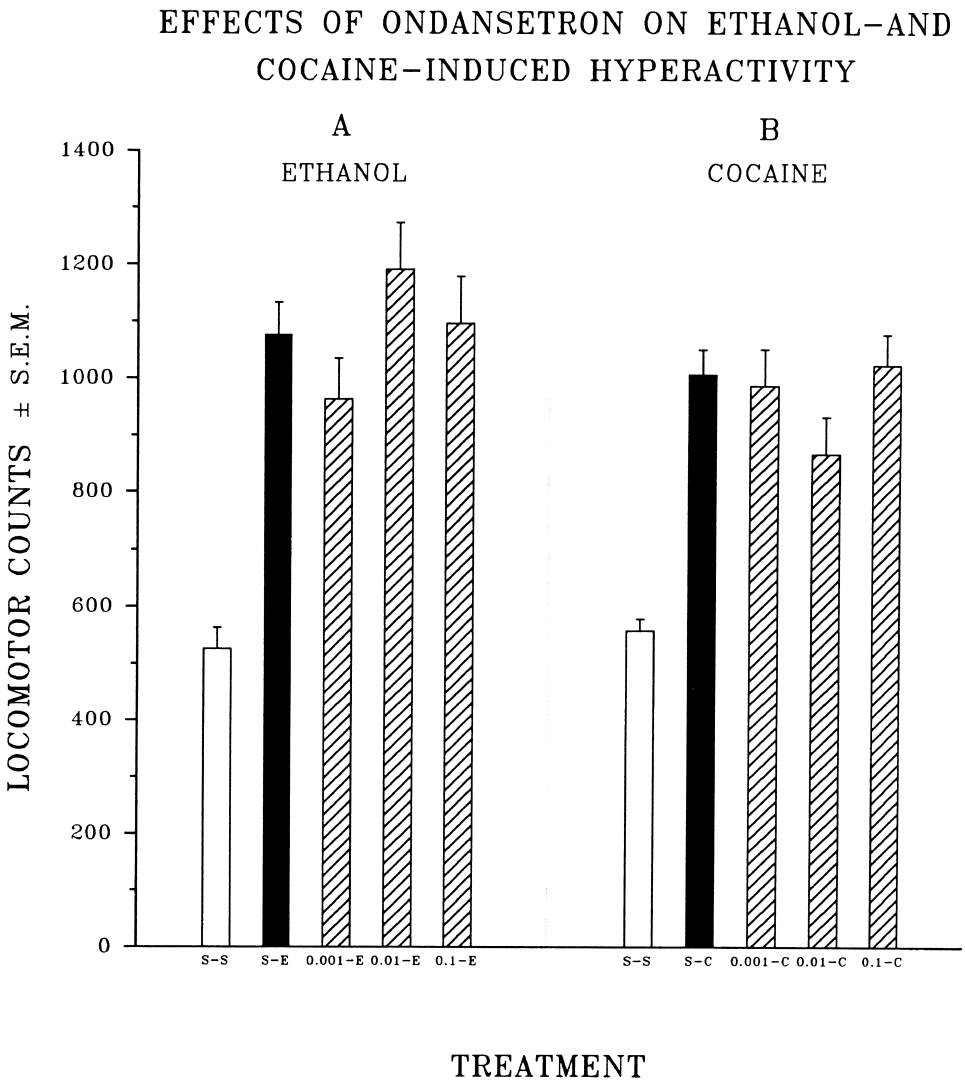

FIG. 2. Effects of pretreatment with various doses of ondansetron on ethanol- (panel a) and cocaine-(panel b) induced hyperactivity in DBA/2N mice. The numbers below the bars reflect doses in mg/kg; S; saline and E: ethanol. $N = 12$ mice per group. Vertical bars reflect positive half of the S.E.M.

assessed in procedure involved prior foot-shock in the study of Rajachandran et al (27), the possibility that MDL 72222 might modify the effects of ethanol on LMA through its anxiolytic effect can not be ruled out (37).

One could argue that the failure to observe any effects of ondansetron and ICS 205-930 on ethanol- and cocaine-induced locomotion might be due to ineffective dose range employed and/or that these drugs might alter baseline activity which might confound their effect on ethanol- and cocaine-induced hyperactivity. Doses of these 5-HT_3 receptor antagonists (0.001 to 0.1 mg/kg), however, have been shown to produce a number of behavioral effects in mice and rats (see (5), for review) including DBA mice (32,33). For example, a dose of 0.001 mg/kg of ondansetron or ICS 205-930 has been shown to inhibit defeat analgesia in DBA mice (32,33). Although, the effects of ondansetron and ICS 205-930 on baseline activity were not examined in the present study, these compounds have been shown to produce no effects on LMA in rats and C57BL/6 mice (7,28,38). Ondansetron in doses of 0.001 to 0.1 mg/kg has also been shown to produce no effect on baseline activity in DBA mice as measured over a period of 10 min in the elevated plus-maze test (31). In a recent study designed to examine the effects of ondansetron and ICS 205-930 on ethanol-induced place preference (22), we found no effects of ondansetron or ICS 205-930 in doses ranging from 0.001 to 1 mg/kg on LMA as measured over a period of 5 min. An examination of the LMA scores of the present study during the first 6 min following either ethanol or cocaine administration during which the most pronounced stimulation of LMA was seen, also reveals no significant differences among various experimental groups.

In agreement with a previous study (1) the present work also shows that D_1 receptors play a more important role than D_2 receptors in cocaine-induced hyperactivity. Since only one single dose of spiperone was employed in the present study, we can not rule out the involvement of D_2 receptor in cocaine-

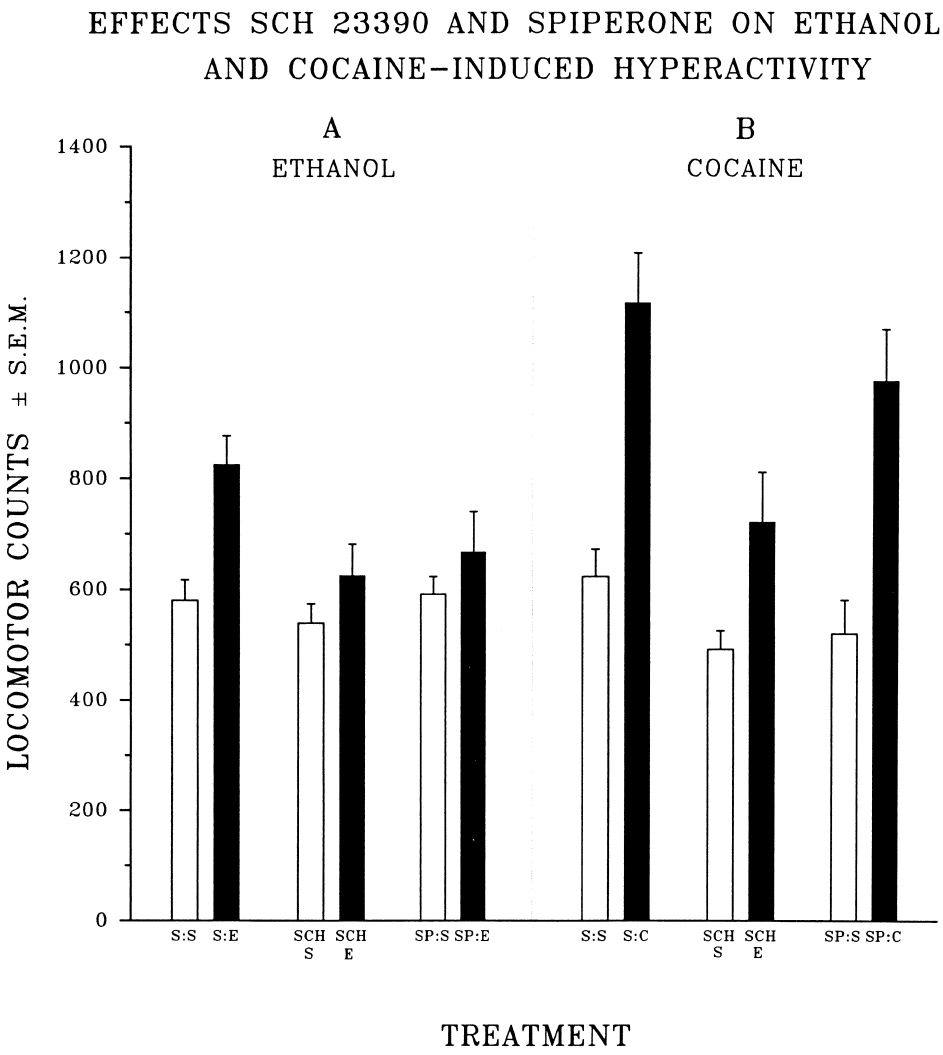

FIG. 3. Effects of pretreatment with SCH23390 and spiperone on ethanol- (panel a) and cocaine- (panel b) induced hyperactivity in DBA/2N mice. N = 10 mice per group. Vertical bars reflect positive half of the SEM.

induced hyperactivity. However, across a wide range of doses of ondansetron or ICS 205-930, no effects of either of these 5-HT_3 antagonists on cocaine induced hyperactivity were observed. In general, 5-HT_3 antagonists have produced inconsistent results in this behavioural paradigm, ranging from minimal suppression in cocaine-induced hyperactivity (39,44) to a significant reversal (28,38). At present it is difficult to reconcile these differences except on the basis of the differences in strain and/or species employed in these studies. However, it is noteworthy that numerous other studies have failed to demonstrate a role played by 5-HT_3 receptors in modifying the discriminative and reinforcing effects of cocaine (24). Most experimental evidence has suggested that 5-HT_3 receptor antagonists may affect DA release via a presynatic mechanism. 5-HT_3 antagonists have been shown to decrease DA firing rates of both A9 and A10 neurons (36). Similarly, 5-HT_3 antagonists only affect the release of DA in the NAcc induced by drugs that affect the firing of DA neurons (2). Tyers et al (42), however, has suggested that 5HT_3 antagonist might have some post synaptic actions as the hyperactivity induced by microinfusion of DA into the NAcc is inhibited by ICS205-930. If 5HT_3 antagonists affect primarily DA neurons firing activity, it is not surprising that the hyperactivity induced by cocaine is not modified by 5-HT_3 antagonist as cocaine exerts its action primarily by blocking the reuptake of DA in its terminals (10). It should be pointed out that 5-HT_3 antagonists have also been shown to produce no effect on cocaine binding sites on DA transporter (38).

In summary, selective blockade of D_1 and D_2 receptors reversed the effects of ethanol- and cocaine-induced hyperactivity. However, the locomotor activating effects elicited by either drug was not influenced by the administration of the 5-HT_3 receptor antagonists, ondansetron and ICS205-930. These results suggest a complex involvement of the DA-ergic system in mediating ethanol-induced hyperactivity. Furthermore, the failure of the 5-HT_3 receptor antagonists to modify the hyperactivity induced by either ethanol or cocaine also brings into question the relationship between the stimulatory and rewarding effects of drugs of abuse. Together, these studies suggest a complex mechanism via which 5-HT_3 receptors

modulate DA activity. The consequences of manipulating the 5-HT_3 receptor system appears to be not only dependent on the drug of abuse being investigated but also upon which aspect of that drugs effects is being examined.

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