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Interactions of Ethanol With Benzodiazepine Receptor Ligands in Tests of Exploration, Locomotion and Anxiety

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LISTER, R. G. *Interactions of ethanol with benzodiazepine receptor ligands in tests of exploration, locomotion and anxiety.* PHARMACOL BIOCHEM BEHAV **31**(3) 761–765, 1988.—The ability of benzodiazepine receptor ligands to modify the behavioral effects of ethanol in tests of exploration, locomotion and anxiety are reviewed. Drugs with inverse agonist activity appear capable of consistently antagonizing the reductions in exploration and anxiety caused by ethanol. In contrast, the locomotor stimulant action of ethanol has appeared relatively insensitive to inverse agonists, suggesting that this effect may not be mediated primarily by an action of ethanol at the benzodiazepine/GABA receptor complex.

Alcohol Benzodiazepine receptor Exploration Motor activity Anxiety Mouse

SINCE the first reports that the imidazodiazepine RO 15-4513 (46) was able to antagonise some of ethanol's behavioral effects (2, 43, 47), there has been considerable interest in whether or not the antagonism is related to this compound's action as a benzodiazepine receptor partial inverse agonist (36,39). There was already a literature documenting the ability of various drugs that antagonise the effects of GABA to reverse the effects of ethanol (18, 20, 22, 26, 45). It is now known that these drugs either act at the picrotoxin site or are antagonists at the GABA-A site on the benzodiazepine/GABA receptor complex (50). It did not seem surprising, therefore, that drugs that reduced the effects of GABA via benzodiazepine binding sites (i.e., benzodiazepine receptor inverse agonists) should produce similar effects. However, some reports suggested that other benzodiazepine receptor inverse agonists were not able to antagonise ethanol's effects and that RO 15-4513 may be unusual in this regard (43,47).

Acutely, ethanol exerts a number of different behavioral effects including hypnosis, hypothermia, ataxia, sedation, anterograde amnesia, locomotor stimulation, anxiolysis, and an anticonvulsant effect. It also possesses reinforcing properties that can lead to long-term abuse. The neurobiological mechanisms underlying these different effects remain poorly understood. For example, it is still unclear which, if any, of these effects are related. One approach that has been taken to examine this issue has been to selectively breed animals for sensitivity (and insensitivity) to one of ethanol's effects, and later to examine whether this differential sensitivity generalizes to ethanol's other behavioral effects [see (6)]. The recent surge of interest in pharmacological methods of antagonising ethanol's effects provides another potential opportunity to dissociate the effects of ethanol on different behaviors. If it were possible to antagonise one behavioral effect of ethanol without affecting another this might provide some evidence that ethanol's effects on the two behaviors were mediated by different neurobiological mechanisms. In this paper we wish to consider whether results obtained using benzodiazepine receptor ligands in combination with ethanol provide any evidence that different mechanisms are involved in ethanol's effects on exploration, locomotion and anxiety.

The data on exploration were obtained using a holeboard apparatus which allows an animal's exploration (head-dipping) to be measured independently of its locomotor activity (14). The data on the motor stimulant action of ethanol were obtained from several paradigms (see below). The data on anxiety have been obtained using a number of different animal models including the social interaction test, a plus-maze test and various conflict paradigms. Tables 1–3 provide a summary of the findings that have been obtained so far.

In each table, benzodiazepine receptor ligands are listed in approximate order of increasing agonist efficacy, compounds with the most marked inverse agonist efficacy at the top, and those with the most marked agonist efficacy (i.e., benzodiazepine-like) at the bottom.

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TABLE 1

THE INTRINSIC EFFECTS OF VARIOUS BENZODIAZEPINE RECEPTOR LIGANDS ON EXPLORATORY BEHAVIOR AND THEIR INTERACTIONS WITH DOSES OF ETHANOL, A BARBITURATE, AND A BENZODIAZEPINE WHICH REDUCE EXPLORATION WHEN ADMINISTERED ALONE

Intrinsic Effect		Effect on Decrease Caused by		
		Ethanol	Barbiturate	Benzodiazepines
[↓↓↓]	DMCM	[↓↓↓]	[↓↓↓]	[↓↓]
↓↓[29]	FG 7142	↓↓[29]	[↓↓]	[↓↓↓]
↓↓[28–30]	RO 15-4513	↓↓[28,29]	↓↓[28]	↓↓↓[28]
—↓[31,32]	RO 15-3505	↓↓[31,32]	↓↓[32]	[↓↓↓]
↑[15,34]	Flumazenil	↓[34]	?	↓↓↓[15,17]
↑[12,34]	ZK 93426	↓[34]	?	[↓↓↓]
—↑[31]	RO 17-1812	↑[31]	[↑]	[↓↓]
↑↓[11, 28, 38]	Diazepam	↑[34]	[↑]	↑↑

↑ Enhancement of effect; ↓ reduction of effect; —no effect.
Where arrows are shown in brackets, these reflect predicted results rather than the results of experiments that have already been performed.

TABLE 2

THE INTRINSIC EFFECTS OF VARIOUS BENZODIAZEPINE RECEPTOR LIGANDS ON LOCOMOTOR ACTIVITY AND THEIR INTERACTIONS WITH DOSES OF ETHANOL, A BARBITURATE, AND A BENZODIAZEPINE WHICH INCREASE LOCOMOTION WHEN ADMINISTERED ALONE

Intrinsic Effect		Effect on Stimulant Action of		
		Ethanol	Barbiturates	Benzodiazepines
[↓↓]	DMCM	[—↓]	[—↓]	[↓↓]
—↓[29]	FG 7142	—↓[29]	[—↓]	[↓↓]
—↓[28–30]	RO 15-4513	—↓[28,29]	—[28]	↓↓[28]
—[31,32]	RO 15-3505	—↓[31,32]	—[32]	[↓↓]
—↑[30,34]	Flumazenil	—[34]	[—]	[↓]
—↑[30,34]	ZK 93426	—↓[34]	[—]	[↓]
↑↑[31]	RO 17-1812	—[31]	[—]	[—]
↑↑↑[28,34]	Diazepam	↓↓[34]	[↓↓]	↑↑

↑ Enhancement of effect; ↓ reduction of effect; —no effect.
Where arrows are shown in brackets, these reflect predicted results rather than the results of experiments that have already been performed.

EXPLORATION

In the first column of Table 1 it can be seen that drugs with inverse agonist activity at benzodiazepine receptors tend to reduce exploration when administered alone, drugs with more marked inverse activity (e.g., RO 15-4513 and FG 7142) producing clearer reductions in exploration than less efficacious compounds such as RO 15-3505. The compounds that have been classified as antagonists (flumazenil and ZK 93426) both tend to slightly increase exploration. The partial agonist RO 17-1812 also tends to increase exploration, and full agonists such as diazepam exert biphasic effects. At low doses, an increase in exploration is observed, but at higher doses, a decrease in exploration is seen (11, 28, 38).

In the second column, it can be seen that although the intrinsic effects of the inverse agonists are in the same direction as a 2 g/kg dose of ethanol, all drugs with partial inverse agonist activity have been found capable of partially antagonising ethanol's effect. The two antagonists (flumazenil and ZK 93426) also partially reverse ethanol's effects. RO 17-1812 and diazepam, which both have agonist effects, enhance rather than reduce ethanol's effects.

In the third column, it can be seen that inverse agonists that are capable of antagonising the effects of ethanol (e.g., RO 15-4513 and RO 15-3505), are also effective against sodium pentobarbital. The effects of flumazenil and ZK 93426 remain to be determined. Diazepam and RO 17-1812 would be expected to enhance rather than reduce the effects of a barbiturate.

In the final column, the effects on the decrease in exploration caused by a high dose of a benzodiazepine are shown. All drugs with partial inverse agonist, or antagonist activity are expected to be able to completely antagonise the effects of the benzodiazepine. It should be noted, however, that we

TABLE 3

THE INTRINSIC EFFECTS OF VARIOUS BENZODIAZEPINE RECEPTOR LIGANDS ON ANXIETY AND THEIR INTERACTIONS WITH DOSES OF ETHANOL, A BARBITURATE, AND A BENZODIAZEPINE WHICH REDUCE ANXIETY WHEN ADMINISTERED ALONE

Intrinsic Effect		Effect on Action of		
		Ethanol	Barbiturates	Benzodiazepines
[↑↑↑]	DMCM	[↓↓↓]	[↓↓↓]	[↓↓↓]
↑↑[4, 9, 41]	FG 7142	↓↓[25,33]	↓↓[42]	↓↓↓[25]
↑↑[3, 21, 33]	RO 15-4513	↓↓[3,33]	↓↓[3]	↓↓↓[3]
↑—[33]	RO 15-3505	—[33]	[—]	[↓↓↓]
↑—[13, 16, 25]	Flumazenil	—[25]	[—]	↓↓↓[1]
↑[12,24]	ZK 93426	[—]	[—]	[↓↓↓]
↓↓[19]	RO 17-1812	[↑]	[↑]	[—]
↓↓↓[25,44]	Diazepam	↓↑	[↓↑]	↑↑↑

↑ Enhancement of effect; ↓ reduction of effect; —no effect.

Where arrows are shown in brackets, these reflect predicted results rather than the results of experiments that have already been performed.

found β-CCE incapable of antagonising the effect of chlordiazepoxide in rats in a holeboard test (10), and other investigators have also found that in tests of sedation where inverse agonists and agonists have similar effects no antagonism is observed (51).

LOCOMOTOR STIMULATION

Several points should be made in discussing the effects of the various benzodiazepine receptor ligands on the locomotor stimulant action of ethanol in mice (Table 2). Firstly, a variety of different methods are used to assess the effects of ethanol on motor activity. Inconsistencies across studies can often be attributed to differences in methodologies. Some of the variables that are critically important include: the duration of the test (8), whether or not the animal is familiar with the test environment (27), the ambient lighting (37), the genetic background of the animal (7), as well as the exact nature of the test. Most of the data shown in Table 2 have been obtained using a short (8 min) holeboard test.

In the first column it can be seen that the partial inverse agonists have little intrinsic effects on locomotor activity, but the partial agonist Ro 17-1812 and diazepam increase it. Data on the ability of these drugs to antagonise the stimulant action of ethanol have been much less consistent than on their abilities to antagonise the other effects of ethanol. In general, the inverse agonists exert little effect on ethanol-induced locomotion. In mice naive to the holeboard, we have found antagonism in some studies (29,31) but not in others (28,32). There is no evidence that RO 15-4513 differs from other inverse agonists in its interaction with ethanol on this measure. In the plus-maze test we have failed to find an antagonism of the ethanol-induced increase in the total number of arm entries by any of the partial inverse agonists tested (33).

Several other investigators have found that RO 15-4513 may not antagonise the motor stimulant effect of ethanol in mice (P. Syapin, personal communication and J. Engel, personal communication), and in some cases benzodiazepine receptor inverse agonists may even enhance the motor stimulant effect of ethanol (H. Becker, personal communication). This latter observation is consistent with reports that various GABA antagonists enhance and GABAmimetics reduce the motor stimulant effect of ethanol (5). The effect of diazepam closely resembles that of the GABAmimetics (34).

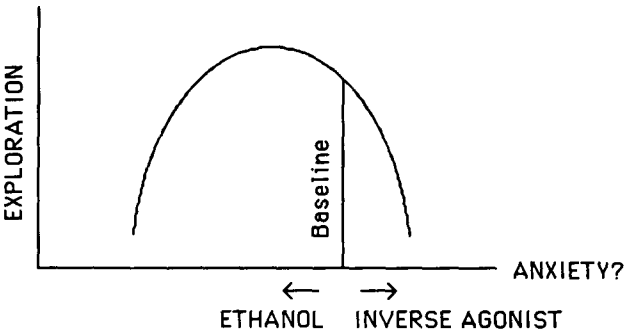

FIG. 1. An example of how ethanol and a benzodiazepine receptor inverse agonist might exert opposite effects in one behavioral dimension yet produce similar effects on exploration.

ANXIETY

Table 3 summarizes the data from a number of studies investigating the anxiolytic effects of ethanol. The effects of the various benzodiazepine receptor ligands alone (shown in the first column) have been thoroughly investigated. In the second and third columns it should be noted that combining a benzodiazepine with ethanol (or a barbiturate) may enhance the anxiolytic effect of each drug at low doses, but a stage is reached where the sedative and psychomotor-impairing effects of the drug combination may lead to increases in anxiety [see, e.g., (35)].

The results shown in Table 3 generally parallel those reported in the seizure threshold model by Nutt and Lister (40). That is, for a drug to antagonise the anxiolytic (or anticonvulsant) effects of ethanol or a barbiturate, it must possess inverse agonist activity [and possess anxiogenic (or proconvulsant) properties].

GENERAL DISCUSSION

In Table 1 it can be seen that ethanol (2 g/kg) and benzodiazepine receptor inverse agonists exert similar effects on exploration, they reduce it. However, when ethanol is combined with an inverse agonist mutual antagonism is observed. A superficial analysis argues against the suggestion that RO 15-4513 antagonises the effects of ethanol by virtue of possessing intrinsic activity opposite to that of ethanol in this paradigm. However, it is important to appreciate that two opposite treatments may alter a behavior in the same direction. For example plots of performance against treatment often reveal an inverted U function. Ethanol's effects on exploration produce such a function, low doses increasing and higher doses decreasing this measure (27). It is, therefore, possible that a benzodiazepine receptor inverse agonist and ethanol exert opposite effects along a dimension that plays a role in exploration (perhaps anxiety), and yet produce the same net result (i.e., decreased exploration). Combining the drugs in these circumstances would produce mutual antagonism. This possibility is illustrated in Fig. 1.

The observation that RO 15-3505 antagonises the effects of ethanol on exploration while possessing no intrinsic effect on this measure may lead the reader to believe that it is a "pure" alcohol antagonist. However, this compound's lack of activity in the holeboard test can be contrasted with its marked proconvulsant activity in the seizure threshold paradigm (40). It raises an important question that must be considered in all studies of the interactions of benzodiazepine receptor inverse agonists with ethanol. If a drug does not appear to be exerting an inverse agonist action in one particular situation does this mean that its effects in combination with ethanol are not mediated by an inverse agonist action? The sensitivity of the test (either biochemical or behavioral) under various conditions may underly the apparent selectivity. Behavioral pharmacologists are often able to manipulate the experimental conditions so that a test is sensitive to one particular effect but not another. For example, the shock level in a conflict paradigm can be altered to allow the test to be sensitive to the effects of anxiolytics (but not anxiogenics) or anxiogenics (but not anxiolytics) (4,44). An antagonism of an anxiolytic effect may then be observed in the absence of an intrinsic anxiogenic effect (44). Of course this does not mean that an anxiogenic action did not mediate the reversal of the anxiolytic effect.

A preliminary comparison of Tables 1–3 suggests that the effects of ethanol on exploration, locomotion, and anxiety may involve different mechanisms. In particular, the comparative lack of effect of inverse agonists on the motor stimulant effect of ethanol contrasts with their abilities to partially reverse the effects of ethanol on exploration and anxiety [and also convulsions (40)]. It is also interesting to note that two groups have failed to antagonise ethanol-induced hypothermia with RO 15-4513 (23,49), suggesting that this effect also may not be mediated through the benzodiazepine/GABA receptor complex.

It is less clear whether the slight differences in the ability of drugs to antagonise the effects of ethanol on exploration, anxiety and seizure threshold are due to different neurobiological mechanisms rather than reflect slight differences in the sensitivities of the tests. The inverse agonists RO 15-4513 and FG 7142 were able to partially antagonise the effects of ethanol on all three measures.

Finally, it should be noted that the effects of the various benzodiazepine receptor ligands in the tests of exploration, locomotion, anxiety, seizure threshold and hypothermia differ from those found using observer-rated tests of intoxication. In these paradigms, RO 15-4513 differs qualitatively from other benzodiazepine receptor inverse agonists in its ability to antagonise the effects of ethanol. Suzdak and coworkers have found that other inverse agonists do not reverse the intoxicating effects of ethanol in rats (47,48). Further, the partial inverse agonists β-CCE and CGS 8216 both reverse (rather than add to) the effect of RO 15-4513 in this paradigm [(48) and see Glowa *et al.*, this issue]. We have found similar results in an observer rated test of ataxia in mice. FG 7142 (20–40 mg/kg) fails to reduce ethanol-induced ataxia, but antagonises the reduction of ethanol's effects by RO 15-4513 (Lister and Durcan, submitted). Clearly further work is needed to clarify why this paradigm differs from the others.

In conclusion, the data discussed above indicate that merely documenting whether or not RO 15-4513 (or any drug) is capable of antagonising the effects of ethanol on one particular behavior is not exceptionally useful. A comparison is needed to determine whether other drugs with similar pharmacological effects are also active, and whether or not the antagonism is observed on other behaviors and against other CNS depressants.

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