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INTRODUCTION

Antagonizing the Behavioral Effects of Ethanol Using Drugs That Act at the Benzodiazepine/GABA Receptor Macromolecular Complex

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IT is more than 50 years since the first reports that drugs such as pentylenetetrazole were able to reverse some of the behavioral effects of anaesthetics, including ethanol. Since then it has become clear that these drugs act at the picrotoxinin site on the benzodiazepine/GABA receptor complex. In the last few years a benzodiazepine receptor partial inverse agonist, RO 15-4513, has also been found capable of antagonizing some of ethanol's effects. It was these latter reports and the controversies surrounding them that led us to organize this symposium. Each speaker was asked to present data on RO 15-4513 and similar compounds in an attempt to address what we consider to be the four critical questions:

1) Which of ethanol's many effects are antagonized?
2) How effectively is each effect antagonized (i.e., is the antagonism complete)?
3) Can the effects of CNS depressants other than ethanol be antagonized (i.e., is the antagonism selective for ethanol)?
4) Does the antagonism result from the intrinsic pharmacological effects of the antagonist (i.e., does the antagonist have pharmacological effects opposite to those of ethanol and the interaction is merely subtractive)?

The participants successfully tackled these questions and although a unanimous consensus was not reached, certain facts emerged:

1) RO 15-4513 has marked intrinsic behavioral effects in both anxiety and seizure paradigms suggestive of a partial inverse agonist.
2) RO 15-4513 is able to reverse some (but not all) of the effects of ethanol and in many tests this reversal is mirrored by other inverse agonists.
3) In two situations RO 15-4513's effects appear different to those of other inverse agonists (in observer-rated intoxication and chloride flux).
4) No compound has yet been tested which acts at the BDZ/GABA receptor complex to reverse the effects of ethanol and is without inverse agonist properties.