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Abstracts

248

DRUG DISCRIMINATION AS A TOOL IN DRUG ABUSE RESEARCH

J.B. Appel.

Drug discrimination (DD) has been useful in elucidating both the basic and clinical pharmacology of abused substances because: 1) the procedure requires organisms to attend to drug-induced changes in their own physiological (internal) state since these changes signal the availability of reinforcement and, 2) abused substances produce particularly potent (and reinforcing) changes in this state. Thus, it has been possible to classify and differentiate drugs on the basis of their discriminable properties; correlate the stimulus effects of drugs with both binding affinities (in animals) and reports of "hallucinations" (in humans); and, most importantly, determine the mechanisms underlying the *in vivo* effects of various opiates (Woods), hallucinogens (Glennon) and PCP- like agents (Balster). Unfortunately, DD has been less successful in describing the actions of CNS stimulants (e.g., cocaine) and "designer" drugs (e.g., MDA and MDMA).

The principle problem with DD or, more accurately, its use, concerns the fact that results (e.g., extent of generalization of a compound to other agonists) often depend on particular parameters (e.g., training drug dose) and procedures (drug-saline vs. drug-drug) as well as the specificity of the agents and techniques used to test hypothesized receptor or neuronal mechanisms. However, in this respect DD is no different from other useful assays (e.g., receptor binding).

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249

MDA: HALLUCINOGEN ? STIMULANT ? BOTH ? OR NEITHER ?

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The hallucinogen- and stimulant- like effects of MDA were studied in groups of rats trained to discriminate either (-) MDA (1.25 mg/kg), (+) MDA (1.25 mg/kg), (+) LSD (0.16 mg/kg), or (+) amphetamine (1.0 mg/kg) from saline. The (-) MDA cue generalized completely to both (+) LSD and DOM, and partially to mescaline and, possibly, cocaine; (+) MDA did not generalize completely to *any* of these compounds. The (-), but not the (+) MDA cue was blocked by the 5-HT_2 antagonist pirenpirone: the DA antagonists Sch-23390 and (-) sulpiride disrupted responding but did not appear to alter the (-) or the (+) MDA cue.

When animals were trained to discriminate prototypic hallucinogens or stimulants from saline, neither LSD (0.16 mg/kg) nor (+) amphetamine generalized more than partially to either (-) or (+) MDA.

These results, in combination with those reported previously, indicate that, at the doses tested, (-) MDA is more similar to hallucinogens and is probably more serotonergic than (+) MDA; neither isomer of MDA seems to have robust, stimulant-like properties.

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250

DISCRIMINATIVE STIMULUS PROPERTIES OF PHENCYCLIDINE AND OTHER NMDA ANTAGONISTS

Robert L. Balster

The pharmacological specificity of the phencyclidine stimulus has been systematically examined. Complete substitution occurs with arylcyclohexylamine analogs of PCP, MK-801, certain sigma-agonist benzomorphans, some dioxolane derivatives, as well as with drugs from a few other novel drug classes. The relationship of this pattern of cross-generalization results to actions at the PCP receptor have clearly implicated this receptor as the cellular basis for PCP discrimination. Despite considerable effort, a reliable antagonist of the PCP stimulus has not been found. Cross-generalization studies with other drug classes show that the PCP stimulus is quite specific for PCP-receptor agonists, with the following exceptions. Some drugs selective for the high-affinity sigma binding site have PCP-like discriminative stimulus effects. In addition, there is some overlap in the stimulus effects of PCP-like drugs and classical CNS depressants such as the barbiturates and alcohol. More recently, some similarities have been found between the discriminative stimulus effects of PCP-like drugs and competitive N-methyl-D-aspartate (NMDA) antagonists, possibly reflecting PCP's proposed noncompetitive NMDA antagonist effects. Nonetheless, the growing evidence for differences as well in the discriminative stimulus effects of competitive and noncompetitive NMDA antagonists may have important implications for medication development in this area. (Research supported by NIDA Grant DA-01442)

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