271

THE DISCRIMINATIVE STIMULUS PROPERTIES OF LSD: SEROTONERGIC AND CATECHOLAMINERGIC INTERACTIONS.

T.F.Meert, P.L.A.J. De Haes and P.C.M. Vermote.

The discriminative stimulus properties of LSD were assessed in rats trained to discriminate 0.16 mg/kg LSD (IP, T-15 min) from saline in a two lever food reinforced drug discrimination test procedure in rats. The test compounds included LSD, DOM, 8-OHDPAT, buspirone, isapirone, TFMPP, Ru-24969, ritanserin, risperidone, R 79 598, haloperidol and prazosin. All compounds were given at 60 min before testing.

In terms of stimulus generalization with 0.16 mg/kg LSD, a complete substitution was observed with LSD (ED_{50}: 0.26 mg/kg), 8-OHDPAT (0.13 mg/kg) and DOM (0.13 mg/kg). Partial generalization was present with buspirone and TFMPP, while all other compounds were inactive. In terms of an antagonism of the discriminative stimulus properties of 0.16 mg/kg LSD, a complete antagonism was observed with ritanserin (ED_{50}: 11.60 mg/kg) and risperidone (0.028 mg/kg); R 79 598 was partially active (up to 60 %). Although haloperidol and prazosin were without any effect on LSD, both compounds potentiated the LSD antagonist properties of ritanserin. The combined treatment of 0.01 and 0.04 mg/kg haloperidol with ritanserin reduced the ED_{50} of ritanserin to 0.39 and 0.22 mg/kg, respectively. Also with 0.01 and 0.04 mg/kg prazosin, a decrease in the ED_{50} of ritanserin to 2.71 and 0.13 mg/kg was obtained.

These results indicate that i) different 5-HT agonists are able to produce a stimulus generalization to LSD and ii) for a potent LSD antagonism, both a 5-HT_2 and catecholamine antagonism is needed.

Janssen Research Foundation, B-2340 Beerse, Belgium.

272

A DRUG DISCRIMINATIVE ANALYSIS OF LORECLEZOLE, A NEW ANTILEPTIC AGENT.

T.F.Meert, P.L.A.J. De Haes and P.C.M. Vermote.

Loreclezole (R 72 063), a new anticonvulsant with a broad-spectrum activity (Wauquier et al., Drug. Dev. Res., 1990, in press), was compared with chlordiazepoxide, clobazam and carbamazepine in two groups of rats trained to discriminate either 5 mg/kg chlordiazepoxide (IP, T-15 min) or 20 mg/kg metrazol (IP, T-15 min) from saline in a two lever food reinforced drug discrimination test procedure in rats. All test compounds were given orally at 60 min before the beginning of the experiment.

In the chlordiazepoxide trained animals, a complete stimulus generalization was observed with chlordiazepoxide, loreclezole and clobazam; the relative order of potency was chlordiazepoxide > loreclezole > clobazam. At doses up to 40 mg/kg, carbamazepine was inactive.

In the metrazol trained rats, there was no stimulus generalization at all. The relative order of potency to antagonize the discriminative stimulus properties of metrazol was chlordiazepoxide > loreclezole > clobazam > carbamazepine (inactive).

Additional experiments, using animal models of anxiety, indicated loreclezole to possess behavioural disinhibitory properties similar to the benzodiazepines. However, as opposed to the benzodiazepines, loreclezole induced less sedative side-effects.

These results are discussed in terms of the use of loreclezole as an antiepileptic agent.

Janssen Research Foundation, B-2340 Beerse, Belgium.

273

APPLICATION OF DRUG DISCRIMINATION TO DEVELOP NEW THERAPEUTIC AGENTS

T.F. Meert and F. Awouters

In the study of new therapeutic agents, the drug discrimination test procedure provides additional information to basic screening tests, especially when training drugs with a complex pharmacological profile are used. Sometimes, drug discrimination tests greatly elucidate interactions of a new compound with various neurotransmitter systems. In the present study R 79 598, a new neuroleptic known to act on central D2 and 5-HT2 receptors, was compared to haloperidol (mainly D2), ritanserin (5-HT2) and risperidone (5-HT2, D2) in four groups of rats trained to discriminate 0.63 mg/kg DOM, 0.16 mg/kg LSD, 10 mg/kg cocaine or 1.25 mg/kg d-amphetamine from saline. In terms of antagonism of the DOM cue, the relative order of potency of the tested drugs was R 79 598 > risperidone > ritanserin > haloperidol (inactive). For antagonism of the d-amphetamine cue, the relative order was R 79 598 > haloperidol > risperidone > ritanserin (inactive). The potency of the tested compounds to antagonize the DOM cue corresponds to the antagonism of tryptamine-induced bilateral convulsions; the antagonism of the d-amphetamine cue resembles the antagonism of apomorphine-induced agitation and stereotyped behaviour. With respect to the LSD cue, the relative order was risperidone > ritanserin > R 79 598 (partial) > haloperidol (inactive). For cocaine antagonism it was R 79 598 > haloperidol = risperidone > ritanserin (inactive). For both the antagonism of LSD and cocaine, no simple relationship with 5-HT2 or D2 antagonism was found. The differences between behavioural and cueing actions of training drugs with a complex pharmacological profile are discussed especially in relation to the central activity of R 79 598.

Janssen Research Foundation, B-2340 Beerse, Belgium

274

TOLERANCE TO THE ANALGESIC, BUT NOT THE "CUE" PROPERTIES OF MORPHINE AFTER BRIEF SOCIAL STRESS

K. A. Miczek

One of the most prominent consequences of the distinctive experience of defeat in a social confrontation is the long-lasting tolerance to the analgesic effects of opiates. The present experiment examined (1) what kind of social experiences lead to morphine tolerance, (2) whether or not the morphine tolerance in defeat-experienced rats extends to the discriminative stimulus and behaviorally suppressive effects of morphine, and (3) how long morphine tolerance lasts after a defeat experience. Male Long-Evans rats were trained in a two-lever task on a Fixed Ratio 10 schedule of milk reinforcement so that responding on one lever was reinforced when the animal was injected i.p. 30 min earlier with 2.5 mg/kg morphine, and reinforcement on the other lever was available in alternate 10-min sessions after administration of saline. Under these conditions, the ED_{50} for the morphine "cue" was 1.5 mg/kg. Additional determinations with higher morphine doses revealed the ED_{50} for the analgesic effects of morphine to be 8.9 mg/kg in the tail-flick assay. Housing the animals singly, pair-housing the males with a female or male partner, each for 3 weeks, did not significantly alter the ED_{50}'s for the morphine cue or analgesia. However, when the animals were exposed to the attacks and threats by a resident rat in 5 5-min encounters, the dose-effect curve for morphine analgesia showed a twofold shift to the right, whereas 3 out of 9 rats responded to the morphine "cue" at lower doses than before. In a separate group of rats, the tolerance to morphine's analgesic effects after defeat in a social confrontation was detected 3 months after this behavioral intervention, whereas no changes in morphine effects on response suppression or "cue" properties were found. These findings provide evidence for development of tolerance and sensitization within the same individual to separate opiate effects, possibly suggesting the involvement of different opiate receptor populations.

Department of Psychology, Tufts University, 490 Boston Ave., Medford, Massachusetts 02155, USA