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Transduction of the discriminative stimulus effects of zolpidem by $GABA_A/\alpha 1$ receptors

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Abstract

Zolpidem is an imidazopyridine with high affinity at γ-aminobutyric $acid_A$ ($GABA_A$) receptors expressing α1 subunits. In squirrel monkeys trained to discriminate a high dose of zolpidem (≥ 3.0 mg/kg) from saline, zolpidem and another $GABA_A/\alpha 1$ receptor-preferring agonist, zaleplon, substituted dose-dependently for zolpidem, whereas the non-selective agonists diazepam and triazolam were did not substitute at any dose tested. These findings offer the first evidence for a selective role of $GABA_A/\alpha 1$ receptors in the interoceptive effects of high doses of zolpidem.

Keywords: Zolpidem; Benzodiazepine; Drug discrimination

Zolpidem is an imidazopyridine that acts as an agonist at benzodiazepine receptors associated with the γ-aminobutyric $acid_A$ ($GABA_A$) receptor ionophore. The receptor-binding profile of zolpidem differs from conventional benzodiazepines in that it displays the highest affinity at $GABA_A$ receptors expressing α1 subunits and relatively low affinity at receptors expressing α2, α3 and α5 subunits (Lüddens et al., 1995). However, when trained as a discriminative stimulus, the effects of zolpidem at low to intermediate doses overlap completely with those of conventional, non-selective benzodiazepines agonists (Sanger and Zivkovic, 1986; Rowlett et al., 1999), suggesting that the discriminative stimulus effects of zolpidem may be mediated at multiple $GABA_A$ receptor subtypes.

Previous research has shown that pharmacological specificity of the discriminative stimulus effects of benzodiazepine agonists can depend critically on the dose of drug used to establish the discrimination (Lelas et al., 2000). In this regard, fewer drugs typically substitute for the training stimulus at high compared to low training doses (Sannerud and Ator, 1995; Lelas et al., 2000). Based on this observation, the present study investigated the apparent specificity of the discriminative stimulus effects of zolpidem in squirrel monkeys trained to discriminate a relatively high dose of zolpidem (≥ 3.0 mg/kg) and then tested with a range of doses of zolpidem, another preferential $GABA_A/\alpha 1$ receptor ligand, zaleplon (Damgen and Lüddens, 1999), and the conventional, non-selective benzodiazepine agonists, triazolam and diazepam.

Four adult male squirrel monkeys (*Saimiri sciureus*), weighing 720–900 g at the beginning of the study, were trained to discriminate zolpidem from saline under a 10-response, fixed ratio schedule of food reinforcement. Procedures used to implant catheters and maintain the discriminative stimulus effects of zolpidem were identical to those described previously (Rowlett et al., 1999), except that the training dose was increased from 1.0 to 3.0 or 5.6 mg/kg. Drug test sessions, in which 10 presses on either lever resulted in delivery of food, were conducted only if ≥ 80% of responses were made on the injection-appropriate lever during at least four of the preceding five training sessions. The ability of a drug to substitute fully for zolpidem was analyzed based on the average maximum of the percentage of drug-lever responding for zolpidem at the training dose. Results from tests with the training dose were averaged for each monkey and a group mean with 95% confidence interval (CI) was computed. A drug was considered to have achieved full substitution if its average zolpidem-lever

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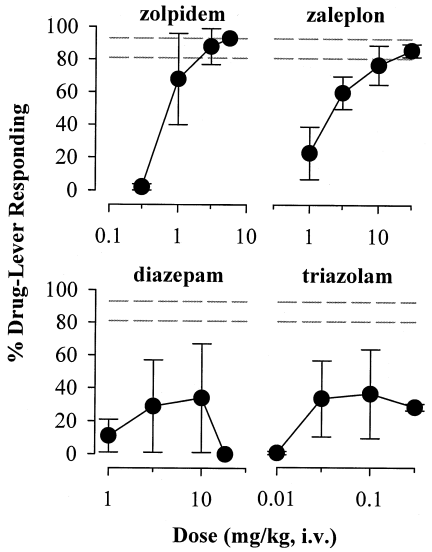

Fig. 1. Discriminative stimulus effects (mean percentage of drug-lever responding ± SEM) of benzodiazepine agonists in squirrel monkeys (N = 4) trained to discriminate 3.0 or 5.6 mg/kg of zolpidem from saline. Dashed horizontal lines represent the 95% CI for percentage of drug-lever responding during test sessions with the training dose of zolpidem.

responding fell within the 95% CI. Mean response rates (responses per second) were calculated for test compounds, and drug-lever responding was calculated only if rates of responding were greater than 0.1 responses/s.

During training, all monkeys responded predominantly on the zolpidem lever (mean = 87%) at either 3.0 or 5.6 mg/kg. Higher training doses were not studied because they severely suppressed or eliminated responding in pilot experiments. Under test conditions, increasing doses of zolpidem engendered corresponding increases in drug-lever responding (Fig. 1), achieving full substitution for the training condition with cumulative test doses of 3.0 mg/kg or higher. Dose-related increases in drug-lever responding and full substitution for the zolpidem-training dose also were observed with zaleplon under identical test conditions (Fig. 1). In contrast, diazepam and triazolam engendered inconsistent zolpidem-lever responding that did not reach zolpidem-like levels up to doses that suppressed responding in at least half the subjects (Fig. 1).

In a previous study in which 1.0 mg/kg of zolpidem was trained as a discriminative stimulus, the non-selective benzodiazepine agonists diazepam and triazolam engendered full zolpidem-appropriate responding (Rowlett et al., 1999), indicating considerable overlap in the interoceptive effects of zolpidem and conventional benzodiazepine agonists. By increasing the training dose of zolpidem, the present study demonstrates an increase in the pharmacological specificity of the zolpidem-discriminative stimulus, based both on the ability of another $GABA_A/\alpha 1$ receptor agonist to substitute for zolpidem and the failure of the non-selective agonists triazolam and diazepam to engender consistent zolpidem-appropriate responding. These findings provide the first evidence for the selective involvement of $\alpha 1$ subtypes of $GABA_A$ receptors in the transduction of the discriminative stimulus effects of zolpidem at high doses. The failure of triazolam and diazepam to engender consistent zolpidem-lever responding also implies that activation of $GABA_A$ receptors expressing subunits other than $\alpha 1$ may be inhibitory with respect to transduction of $\alpha 1$-mediated discriminative stimulus effects.

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Animals in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and the "Guide for Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare Publication No. (NIH) 85-23, revised 1996. Research protocols were approved by the Harvard Medical School Institutional Animal Care and Use Committee.

References

Damgen, K., Lüddens, H., 1999. Zaleplon displays a selectivity to recombinant GABA(A) receptors different from zolpidem, zopiclone and benzodiazepines. Neurosci. Res. Commun. 25, 139–148.

Lelas, S., Spealman, R.D., Rowlett, J.K., 2000. Using behavior to elucidate receptor mechanisms: a review of the discriminative stimulus effects of benzodiazepines. Exp. Clin. Psychopharmacol. 8, 294–311.

Lüddens, H., Korpi, E.R., Seeburg, P.H., 1995. $GABA_A$/benzodiazepine receptor heterogeneity: neurophysiological implications. Neuropharmacology 34, 245–254.

Rowlett, J.K., Spealman, R.D., Lelas, S., 1999. Discriminative stimulus effects of zolpidem in squirrel monkeys: comparison with conventional benzodiazepines and sedative-hypnotics. J. Pharmacol. Exp. Ther. 291, 1233–1241.

Sanger, D.J., Zivkovic, B., 1986. The discriminative stimulus properties of zolpidem, a novel imidazopyridine hypnotic. Psychopharmacology 89, 317–322.

Sannerud, C.A., Ator, N.A., 1995. Drug discrimination analysis of midazolam under a three-lever procedure: II. differential effects of benzodiazepine receptor agonists. J. Pharmacol. Exp. Ther. 275, 183–193.