Available online at www.sciencedirect.com
SCIENCE DIRECT
Pharmacology, Biochemistry and Behavior 83 (2006) 21 – 27
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

# Acute zolpidem administration produces pharmacodynamic and receptor occupancy changes at similar doses

Jeanne M. Fahey [a,*], Jeffrey M. Grassi [b], Jyoti M. Reddi [a], David J. Greenblatt [a]

[a] *Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine and the Division of Clinical Pharmacology, Tufts-New England Medical Center, 136 Harrison Avenue, Boston, MA 02111, USA*
[b] *Vertex Pharmaceuticals Incorporated, Cambridge, MA 02139, USA*

Received 20 April 2005; received in revised form 2 December 2005; accepted 6 December 2005
Available online 24 January 2006

**Abstract**

Zolpidem is chemically unrelated to classical benzodiazepines but has demonstrated relatively high affinity binding to the $\alpha_1$ $GABA_A$ receptor. To assess pharmacodynamic and neurochemical effects of zolpidem, open-field behavior, pentylenetetrazole-induced seizure threshold and benzodiazepine receptor binding in vitro were evaluated in the same animal following a single dose of zolpidem. Zolpidem (2, 5 and 10 mg/kg), lorazepam (2 mg/kg) or vehicle was administered intraperitoneally in male CD-1 mice. Behavioral activity, assessed by three open-field parameters, was decreased following the two highest doses of zolpidem (5 and 10 mg/kg), and reached significance at the 10 mg/kg dose. Locomotor activity was also decreased significantly by lorazepam as expected. Pentylenetetrazole-induced seizure threshold was increased with the administration of 2 and 10 mg/kg zolpidem as well as with lorazepam. Apparent affinity ($K_D$) of [$^3$H]flunitrazepam, a non-selective ligand, for the benzodiazepine receptor in cortical membrane preparations was not significantly changed, while receptor number ($B_{max}$) was decreased at all doses of zolpidem, reaching significance at the 10 mg/kg dose. These results confirm that the behavioral effects of zolpidem are similar to those of classical benzodiazepines. In addition, zolpidem had no significant effect on the affinity of the benzodiazepine receptor for [$^3$H]flunitrazepam, but did decrease the density of receptor binding sites.


*Keywords:* Behavior; Benzodiazepine; GABA; Zolpidem; Pentylenetetrazole-induced seizures

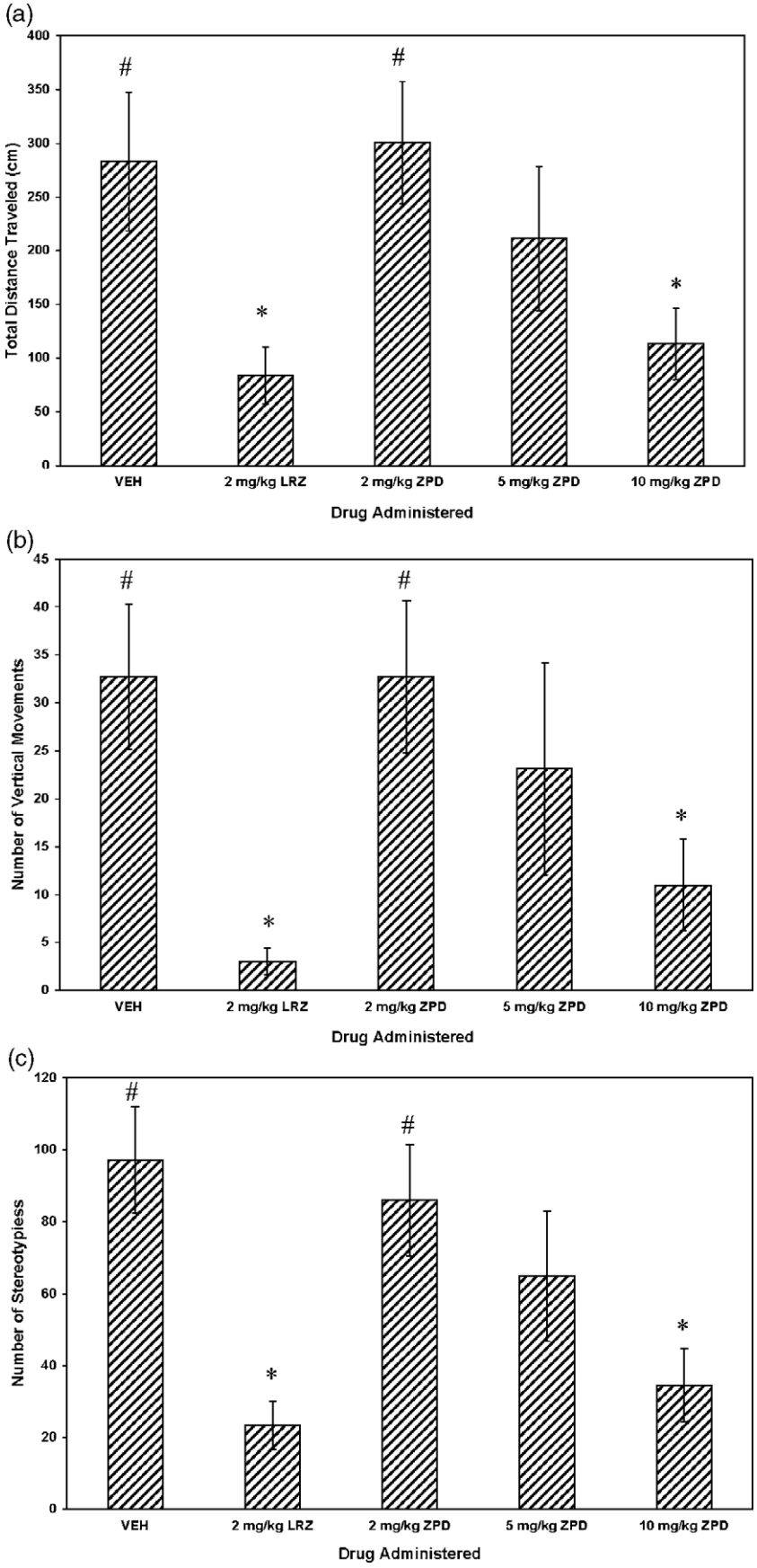
## 1. Introduction

Introduced into clinical practice in the United States in 1992, zolpidem is now the most commonly prescribed hypnotic due to its clinical efficacy, safety, ability to be well tolerated and favorable pharmacokinetic profile (Langtry and Benfield, 1990; Rush, 1998). Although structurally unrelated to benzodiazepines, the imidazopyridine zolpidem produces its effects at the benzodiazepine binding site on the $GABA_A$ receptor (Sanger et al., 1994). Zolpidem binds to the benzodiazepine-$GABA_A$ receptor complex with an affinity that depends on α subunit composition (Ruano et al., 1992). Three zolpidem binding sites have been demonstrated in the adult rat brain: a high affinity site on $\alpha_1$-containing $GABA_A$ receptors ($K_i$=20 nM), a low affinity site on $\alpha_2$ and $\alpha_3$-containing $GABA_A$ receptors ($K_i$=400 nM) and a very low affinity site on $\alpha_5$-containing $GABA_A$ receptors ($K_i$>5000 nM) (Benavides et al., 1993; Langer et al., 1992; McKernan et al., 1991; Mertens et al., 1993; Pritchett and Seeburg, 1990; Ruano et al., 1992). This is in direct contrast to classical benzodiazepines which bind all $GABA_A$ receptors with similar affinity and are, therefore, non-selective (Langer and Arbilla, 1988).

There are few studies to date which have examined the sedative and anticonvulsant effects of acute zolpidem treatment in the same animal. Several investigators have separately established that acute administration of the imidazopyridines produces decreased locomotor activity. Sanger et al. (1986) demonstrated that acute administration of zolpidem decreased locomotor activity in mice at doses ranging from 0.25 to 2 mg/kg. Elliot and White (2001) also demonstrated a sedative effect of zolpidem in rats at doses of 5 and 10 mg/kg. Other investigators have examined both sedative and anticonvulsant effects of

* Corresponding author. Tel.: +1 617 636 4054; fax: +1 617 636 6738.
*E-mail address:* jeanne.fahey@tufts.edu (J.M. Fahey).

0091-3057/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2005.12.006


(a)
Total Distance Traveled (cm)
400
350
300
250
200
150
100
50
0
#
#
*
*
VEH
2 mg/kg LRZ
2 mg/kg ZPD
5 mg/kg ZPD
10 mg/kg ZPD
Drug Administered
(b)
Number of Vertical Movements
45
40
35
30
25
20
15
10
5
0
#
#
*
*
VEH
2 mg/kg LRZ
2 mg/kg ZPD
5 mg/kg ZPD
10 mg/kg ZPD
Drug Administered
(c)
Number of Stereotypiess
120
100
80
60
40
20
0
#
#
*
*
VEH
2 mg/kg LRZ
2 mg/kg ZPD
5 mg/kg ZPD
10 mg/kg ZPD
Drug Administered