

Project Number:	5R01DA011792-12	Contact Principal Investigator:	ROWLETT, JAMES K
Title:	ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	Awardee Organization:	HARVARD UNIVERSITY (MEDICAL SCHOOL)

Abstract Text:

DESCRIPTION (provided by applicant): Benzodiazepines (BZs) are prescribed widely for the treatment of anxiety and sleep disorders. Although BZs are considered to be among the safest prescription drugs in modern medicine, their utility is constrained by a number of side effects, including the liability for abuse and dependence, and recent epidemiological research suggests BZ abuse is on the rise in the U.S. The overall goal of this application is to investigate the extent to which GABAA receptor subtypes are differentially involved in the anxiolytic effects, self-administration, and physical dependence associated with BZ ligands, using relevant nonhuman primate models. Ligands with selectivity for different BZ-sensitive receptors (i.e., 11GABAA, 12GABAA, 13GABAA, and 15GABAA subtypes) will be used as pharmacological probes to determine the role of these receptors in the behavioral effects of BZs. Anxiolytic activity will be evaluated in rhesus monkeys using conflict procedures in which food-maintained behavior is concurrently suppressed by response-produced presentations of an aversive stimulus. Reinforcing effects will be evaluated using progressive-ratio schedules of i.v. drug self-administration. Physical dependence and tolerance following chronic BZ treatment will be measured using quantitative observation techniques. For all procedures, systematic antagonism studies will be used to dissociate effects due to specific GABAA receptor subtypes. Identification of compounds that are effective anxiolytics lacking abuse and dependence potential in our studies will provide fundamental information for developing safer and more broadly effective anti-anxiety medications, as well as compounds that may be beneficial in the pharmacological management of BZ dependence. PUBLIC HEALTH RELEVANCE: Valium and related drugs, referred to as "benzodiazepines" are prescribed widely for the treatment of anxiety and sleep disorders, two of the most common psychiatric disorders in the U.S. Benzodiazepines are considered to be among the safest prescription drugs in modern medicine, but they unfortunately are also drugs of abuse. The overall goal of this application is to uncover brain mechanisms that control the beneficial effects as well as the abuse of benzodiazepines, with the hope of developing safer drugs for treating anxiety and sleep disorders.

Public Health Relevance Statement:

Valium and related drugs, referred to as "benzodiazepines" are prescribed widely for the treatment of anxiety and sleep disorders, two of the most common psychiatric disorders in the U.S. Benzodiazepines are considered to be among the safest prescription drugs in modern medicine, but they unfortunately are also drugs of abuse. The overall goal of this application is to uncover brain mechanisms that control the beneficial effects as well as the abuse of benzodiazepines, with the hope of developing safer drugs for treating anxiety and sleep disorders.

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History:

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Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
5R01DA011792-12		ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2010	NIDA	NIDA	\$343,530
2R01DA011792-11		ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2009	NIDA	NIDA	\$347,000
3R01DA011792-11S1		ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2009	NIDA	NIDA	\$347,000
5R01DA011792-10		ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2008	NIDA	NIDA	\$274,816
5R01DA011792-09		ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2007	NIDA	NIDA	\$280,425
5R01DA011792-08		ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2006	NIDA	NIDA	\$288,801
5R01DA011792-07		ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2005	NIDA	NIDA	\$295,750
2R01DA011792-06A1		ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2004	NIDA	NIDA	\$253,500

5R01DA011792-05	ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2002	NIDA	NIDA	\$246,371
5R01DA011792-04	ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2001	NIDA	NIDA	\$239,195
5R01DA011792-03	ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	2000	NIDA	NIDA	\$232,226
5R01DA011792-02	ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	1999	NIDA		
1R01DA011792-01	ANXIOLYTIC EFFECTS AND ABUSE OF BZ RECEPTOR LIGANDS	ROWLETT, JAMES K	HARVARD UNIVERSITY (MEDICAL SCHOOL)	1998	NIDA		

Anti-conflict effects of benzodiazepines in rhesus monkeys: relationship with therapeutic doses in humans and role of GABAA receptors.

Rowlett JK, [Lelas S](#), [Tornatzky W](#), [Licata SC](#).

[Psychopharmacology \(Berl\)](#). 2006 Jan;184(2):201-11. Epub 2005 Dec 24.

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Abstract

RATIONALE AND OBJECTIVES: Conflict procedures are used to study mechanisms underlying the anxiolytic effects of benzodiazepines (BZs). We established a conflict procedure with rhesus monkeys in order to examine the role of GABAA receptors in the anxiolytic-like effects of BZs.

METHODS: Four rhesus monkeys responded under a two-component multiple schedule in which responding was maintained under a fixed-ratio schedule of food delivery in the absence (non-suppressed responding) and presence (suppressed responding) of response-contingent electric shock.

RESULTS: Conventional BZs (alprazolam, flunitrazepam, clonazepam, nitrazepam, lorazepam, bromazepam, diazepam, flurazepam, clorazepate, chlordiazepoxide) engendered increases in the average rates of suppressed responding at low to intermediate doses and decreased the average rates of non-suppressed responding at higher doses. Positive correlations were observed when the therapeutic potencies of BZs in humans were compared with potencies to increase the rates of suppressed responding ($R^2=0.83$) or decrease the rates of non-suppressed responding ($R^2=0.60$). The 5-HT_{1A} agonist buspirone increased the rates of suppressed responding, although the effects were modest, whereas the opioid morphine lacked anti-conflict effects. The BZ antagonist flumazenil also modestly increased the rates of suppressed responding. A relatively low dose of flumazenil enhanced, while a high dose blocked, alprazolam's anti-conflict effects. Compounds selective for alpha1 subunit-containing GABAA receptors (zolpidem, zaleplon, CL218,872) engendered relatively weak increases in the rates of suppressed responding.

CONCLUSIONS: A rhesus monkey conflict procedure was established with predictive validity for therapeutic doses in people and provided evidence that anxiolytic-like effects of BZs can occur with relatively low intrinsic efficacy at GABAA receptors and are reduced by alpha1GABAA receptor selectivity.