Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 463 (2003) 3–33
www.elsevier.com/locate/ejphar

The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review

Laetitia Prut, Catherine Belzung*

EA3248, Psychobiologie des Émotions, Faculte des Sciences et Techniques, Universite Francois Rabelias, Parc de Grandmont Avenue Monge, 37200 Tours, France

Accepted 10 December 2002

Abstract

The open field is a very popular animal model of anxiety-like behavior. An overview of the literature on the action elicited by effective or putative anxiolytics in animal subjected to this procedure indicates that classical treatments such as benzodiazepine receptor full agonists or 5-HT_{1A} receptor full or partial agonists elicit an anxiolytic-like effect in this procedure in most cases (approximately 2/3). However, compounds (triazolobenzodiazepines such as adinazolam and alprazolam, selective serotonin reuptake inhibitors) that have a different spectrum of therapeutic efficacy in anxiety disorders such as panic attacks, generalized anxiety disorder or obsessive-compulsive disorder were poorly effective as anxiolytics in the open field test, suggesting that this paradigm may not model features of anxiety disorders. The procedure is also relevant for the study of compounds endowed with anxiogenic effects, as such effects were detected after treatments with benzodiazepine receptor inverse agonists or with corticotropin releasing factor (CRF) receptor agonists.

Keywords: Open field; Benzodiazepine; 5-HT (5-hydroxytryptamine: serotonin); Neuropeptide; Anxiety

1. Introduction

Hall (1934) originally described the open field test for the study of emotionality in rats. The procedure consists of subjecting an animal, usually a rodent, to an unknown environment from which escape is prevented by surrounding walls (Walsh and Cummins, 1976). Hall's apparatus consisted of a brightly illuminated circular arena of about 1.2 m diameter closed by a wall 0.45 m high. He placed rats individually in the outer ring of the open field and observed the rat's behavior for 2 min, during daily repeated trials. Rats were sometimes tested after 24 or 48 h food deprivation. Hall observed that rats walked more when they were food deprived, but not all rats ate. Animals that did not eat were termed emotional. When compared to non-emotional rats, they had fewer entries in the central part of the arena and higher levels of defecation.

The open field test is now one of the most popular procedure in animal psychology (see Belzung, 1999 for a review). Different versions are available, differing in shape of the environment (circular, square or rectangular), lighting (lighting from above with a bulb above the open field or lighting from underneath with a bulb placed under a transparent floor, sometimes red light is used), presence of objects within the arena such as platforms, columns, tunnels (see for example Takahashi and Kalin, 1989), etc. The procedure generally usually involves forced confrontation of a rodent with the situation. The animal is placed in the center or close to the walls of the apparatus and the following behavioral items are recorded for a period ranging from 2 to 20 min (usually 5 min): horizontal locomotion (number of crossings of the lines marked on the floor), frequency of rearing or leaning (sometimes termed vertical activity), grooming (protracted washing of the coat). In such a situation, rodents spontaneously prefer the periphery of the apparatus to activity in the central parts of the open field. Indeed, mice and rats walk close to the walls, a behavior called thigmotaxis. Increase of time spent in the central part as well as of the ratio central/total locomotion or decrease of the latency to enter the central part are indications of anxiolysis. Some authors use a procedure in which the animals are allowed free access to the open field, from a familiar cage (see for example Kopp et al., 1997). In this case, the number of risk assessment postures directed to the

* Corresponding author. Tel.: +33-2-47-36-69-94; fax: +33-2-47-36-72-85.
E-mail address: belzung@univ-tours.fr (C. Belzung).

0014-2999/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0014-2999(03)01272-X

Table 1
Effects of benzodiazepines and other $GABA_A$ pentamer ligands on animals subjected to the open field test

Drug	Mechanisms	Animals	Doses	Routes	Effects	Comments	Reference
Abecarnil	Benzodiazepine receptor α1 selective agonist	Wistar rats	0.01–0.3 mg/kg	i.p., 5 ml/kg	+		Rex et al., 1996
Abecarnil	Benzodiazepine receptor α1 selective agonist	Wistar rats	0.01–0.3 mg/kg	i.p.	0		Nazar et al., 1997
Adinazolam	Triazolobenzodiazepine, Benzodiazepine receptor agonist (its metabolite NDMAD potent as benzodiazepine receptor agonist)	Sprague–Dawley rats	1.5–5 mg/kg	route? twice daily, for 12 days	0	–bilaterally bulbectomized rats –chronic treatment	O'Connor et al., 1985
Adinazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist (its metabolite NDMAD potent as benzodiazepine receptor agonist)	Sprague–Dawley rats	1.5–5 mg/kg	route? twice daily, for 12 days	0	–sham rats –chronic treatment	O'Connor et al., 1985
Adinazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist (in fact, its metabolite NDMAD potent as benzodiazepine receptor agonist)	Sprague–Dawley rats	1st hour: 10 mg/kg 2nd hour: 2 mg/kg	i.p.	+		Broderick et al., 1998
Allopregnanolone	Neurosteroid binding to $GABA_A$ receptor pentamer	Sprague–Dawley rats	500 ng	bilaterally infused in the midbrain central gray	0	ovariectomized estradiol benzoate-treated rats	McCarthy et al., 1995
Allopregnanolone	Neurosteroid binding to $GABA_A$ receptor pentamer	Wistar rats	5 and 10 μg/4μl	i.c.v.	–		Czlonkowska et al., 1999
Alpidem	Selective benzodiazepine receptor α1 receptor partial agonist	Wistar rats	0.1–1–10 mg/kg	i.p.	0		Nazar et al., 1997
Alprazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist	Sprague–Dawley rats	2.5–5 mg/kg	route? twice daily, for 12 days	0	–bilaterally bulbectomized rats –chronic treatment	O'Connor et al., 1985
Alprazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist	Sprague–Dawley rats	2.5–5 mg/kg	route? twice daily, for 12 days	0	–sham rats –chronic treatment	O'Connor et al., 1985
Alprazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist	CD1 mice	0.02 mg/kg	i.p.	+		Lopez et al., 1988
Alprazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist	CD1 mice	0.05 mg/kg	i.p.	–		Lopez et al., 1988

Alprazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist	mice	2 mg/kg/day	osmotic pump; 1–14 days	0	–decrease activity after 1 and 2 days –day 4 to 14: tolerance	Miller et al., 1989b
Alprazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist	CD-1 mice	0.2 mg/kg/day	i.p., for 14 days	0	chronic treatment	Lopez et al., 1992
Barbitol	Barbiturate agonist	Wistar rats	40–60–80 mg/kg	route?	–	decrease frequency of grooming	Barros et al., 1994
β-CCB (*n*-butyl β carboline-3-carboxylate)	Benzodiazepine receptor inverse agonist	A_2G mice	1 to 30 mg/kg	i.p.	–	Dose-dependent	Novas et al., 1988
β-CCB (*n*-butyl β carboline-3-carboxylate)	Benzodiazepine receptor inverse agonist	A_2G mice	3 to 30 mg/kg	i.p.	0	decreased nb of rearings	Novas et al., 1988
β-CCE (ethyl β-carboline-3-carboxylate)	Benzodiazepine receptor partial inverse agonist	Long–Evans rats	10 mg/kg	s.c.	–	Sham-lesioned rats	Podhorna and Franklin, 2000
β-CCM (β-carboline-3-carboxylic acid-*N*-methylamide)	Benzodiazepine receptor inverse agonist	Chickens (*Gallus gallus*)	2.5 mg/kg	i.p.	–		Moriarty, 1995
β-CCM	Benzodiazepine receptor inverse agonist	Wistar rats	0.1–0.5–5 mg/kg	i.p.	–		Nazar et al., 1997
Bicuculline	$GABA_A$ receptor antagonist	Wistar rats	0.25 mg/kg	i.p.	0		Car et al., 1996
Bretazenil (Ro 16-6028)	Benzodiazepine receptor partial agonist	Hooded rats	1–10 mg/kg	i.p.	+	increased rearings and decreased groomings at high dose	Yerbury and Cooper, 1987
Bretazenil	Benzodiazepine receptor partial agonist	mice	0.25, 1 and 4 mg/kg/day	implanted s.c. osmotic pump	0	–dose-dependent –decrease rearings	Miller et al., 1990
Bretazenil	Benzodiazepine receptor partial agonist	Wistar rats	0.1–1–10 mg/kg	i.p.	0		Nazar et al., 1997
Bretazenil	Benzodiazepine receptor partial agonist	Wistar rats	10 μg/site	in the dentate gyrus of the dorsal hippocampus	0	inhibit motor activity	Nazar et al., 1999a,b
Bretazenil	Benzodiazepine receptor partial agonist	Sprague–Dawley rats	200 and 300 μg/kg	i.p.	0	decrease activity (square crossing)	Tashma et al., 2001
Brotizolam	Thienotriazolobenzodiazepine, benzodiazepine receptor agonist	Wistar rats	0.5 mg/kg	p.o.	+		Ueki et al., 1984

(continued on next page)

Table 1 (*continued*)

Drug	Mechanisms	Animals	Doses	Routes	Effects	Comments	Reference
Brotizolam	Thienotriazolobenzodiazepine, benzodiazepine receptor agonist	Wistar rats	1–2 mg/kg	p.o.	0		Ueki et al., 1984
Brotizolam	Thienotriazolobenzodiazepine, benzodiazepine receptor agonist	Wistar rats	5 mg/kg	p.o.	−		Ueki et al., 1984
Chlor-desmethyldiazepam	Benzodiazepine receptor full agonist	Swiss-NOS mice	0.08–1.25–5 mg/kg	i.p.	0.08: 0 1.25: + 5: −	at 5 mg/kg: sedative effect	De Angelis et al., 1982
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley rats	20 and 30 mg/kg	s.c., in 1 ml/kg	+	single food pellet in the center of a new open field environment	Britton and Britton, 1981
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	NIH albino mice	5, 10, 30 and 50 mg/kg	i.p., in 5 ml/kg	+		Crawley, 1981
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	Inbred rats F344	1 mg/kg	i.p., on days 1–21 of pregnancy (perinatally)	0	−activity minimally affected −chronic treatment	Adams, 1982
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	rats	3 mg/kg	i.p.	+		Sanger and Zivkovic, 1988
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	rats	30 mg/kg	i.p.	0	decreased locomotion	Sanger and Zivkovic, 1988
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	5 mg/kg	i.p.	0	−nonhabituated rats −increased locomotion	Gentsch et al., 1989
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	5 mg/kg	i.p.	0	habituated rats	Gentsch et al., 1989
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	100 μg/kg and 0.1 mg/kg	i.p.	+		Bruhwyler, 1990
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley rats	3.75–5–7.5–10 mg/kg	i.p.	+		Horvath et al., 1992
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley rats	2.5,5,10 mg/kg	i.p., 1 ml/kg during 5 days	+	−dose sensitivity −chronic treatment	Angrini et al., 1998

Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	CF1 mice	5 and 10 mg/kg	i.p.	?	–switch from "high explore" to "high walk" –reduced stretched posture and increased wall-following	Choleris et al., 2001
Chlordiazepoxide	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	1,5,10 mg/kg	i.p.	0	rats exposed to a single session of foot shocks or exposed to the grid cage without shock	Bruijnzeel et al., 2001
CL 218,872	Triazolopyridazine, benzodiazepine receptor partial agonist	Long–Evans rats	10–20 mg/kg	i.p. in 2 ml/kg	+	1 and 5 mg/kg doses have no effect	McNamara and Skelton, 1992
Clonazepam	Triazolobenzodiazepine, benzodiazepine receptor agonist	NIH albino mice	0.1, 0.5 and 5 mg/kg	i.p., in 5 ml/kg	+		Crawley, 1981
Clonazepam	Triazolobenzodiazepine, benzodiazepine receptor agonist	CD1 mice	0.02–0.05 mg/kg	i.p.	–	dose dependent	Lopez et al., 1988
Clonazepam	Triazolobenzodiazepine, benzodiazepine receptor agonist	CD-1 mice	1.5 mg/kg/day	for 1–14 days	days 1, 2 and 4: – days 7 and 14: 0	chronic treatment	Galpern et al., 1991
Clonazepam	Triazolobenzodiazepine, benzodiazepine receptor agonist	Wistar rats	0.1–0.2–0.4–0.8 mg/kg	route?	+	decrease frequency of grooming	Barros et al., 1994
Crotoxin (*Crotalus durissus terrificus* venom)	Benzodiazepine receptor inverse agonist	Wistar rats	100, 250 and 500 μg/kg	i.p.	–		Moreira et al., 1996
Crotoxin	Benzodiazepine receptor inverse agonist	Wistar rats	100, 250 and 500 μg/kg	i.p.	–		Moreira et al., 2000
Desmethyldiazepam	Benzodiazepine receptor agonist, metabolite of diazepam	Swiss-NOS mice	0.16–1.25–5 mg/kg	i.p.	0.16: 0 1.15: + 5: –	at 5 mg/kg: sedative effect	De Angelis et al., 1982
DHEA (dehydroepiandrosterone)	Neurosteroid binding to $GABA_A$ receptor pentamer	Long–Evans rats	0, 3, or 7.5 mg/kg	s.c.	0	decreased activity	Frye and Lacey, 1999
5-androstan-3β-ol-17-one sulfate (dihydroepiandrosterone sulfate = DHEAS)	Neurosteroid binding to $GABA_A$ receptor pentamer	Long–Evans rats	3.2 and 6.4 mg/kg	s.c. and i.c.v.	0	ovariectomized rats	Frye and Sturgis, 1995
DHEAS	Neurosteroid binding to $GABA_A$ receptor pentamer	Wistar rats	5 and 20 mg/kg	s.c.	0		Reddy et al., 1998

(continued on next page)

Table 1 (*continued*)

Drug	Mechanisms	Animals	Doses	Routes	Effects	Comments	Reference
DHEAS	Neurosteroid binding to $GABA_A$ receptor pentamer	Long–Evans rats	0, 3, or 7.5 mg/kg	s.c.	0	decreased activity	Frye and Lacey, 1999
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats, male	5 and 10 mg/kg	s.c., from days 5 to 45 of life; 0.03–0.05 ml from days 5 to 25 and 0.06–0.1 ml from days 26 to 45	0	–chronic treatment –increased ambulation –decreased defecation	Fonseca et al., 1976
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats, female	5 and 10 mg/kg	s.c., from days 5 to 45 of life; 0.03–0.05 ml from days 5 to 25 and 0.06–0.1 ml from days 26 to 45	–	–chronic treatment –decreased ambulation –increased defecation	Fonseca et al., 1976
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Mongolian gerbils (*Meriones unguiculatus*)	8 mg/kg	i.p., 0.34 ml per gerbil	–		Jarbe and Johansson, 1977
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	NIH albino mice	0.5, 2, 5, 10 and 25 mg/kg	i.p., in 5 ml/kg	+	at 25 mg/kg: sedation	Crawley, 1981
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley albino rats	1.5 mg/kg	s.c., in 1 ml/kg	+	single food pellet in the center of a new open field environment	Britton and Britton, 1981
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	2.5, 5, 10 mg/kg/day	s.c., for 16 days of pregnancy	–longer latencies –decreased rearings	chronic treatment	Gai and Grimm, 1982
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	inbred strain rats	2.5 mg/kg	p.o.	+		Matsubara and Matsushita, 1982
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	inbred strain rats	20 mg/kg	p.o.	0	reduced activity	Matsubara and Matsushita, 1982
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	inbred strain rats	2.5, 5, 10 and 20 mg/kg	p.o., repeated for 2, 4, 7 and 14 days	+		Matsubara and Matsushita, 1982
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.025, 0.05, 0.1 g/kg	s.c.	+		Hard et al., 1985
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley rats	2.5 mg/kg	route? twice daily, for 12 days	0	–bilaterally bulbectomized rats –chronic treatment	O'Connor et al., 1985

Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	inbred strains rats	2.5 mg/kg	route? twice daily, for 12 days	0	−sham rats −chronic treatment	O'Connor et al., 1985
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	inbred strains rats	1−5 mg/kg	p.o.	+		Delini-Stula and Hunn, 1988
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	A_2G mice	0.3 mg/kg	i.p.	+		Novas et al., 1988
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	rats	2.5 mg/kg/day	prenatally or postnatally	+		Guillamon et al., 1990
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	inbred strains rats	100 μg/kg	i.p.	0	inhibition of ambulation	Bruhwyler, 1990
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague−Dawley rats	1 mg/kg	i.p.	0	non-stressed rats	Pohorecky and Roberts, 1991
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague−Dawley rats	5 mg/kg	i.p.	−	non-stressed rats	Pohorecky and Roberts, 1991
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague−Dawley rats	1 mg/kg	i.p.	+	stressed rats	Pohorecky and Roberts, 1991
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague−Dawley rats	5 mg/kg	i.p.	−	stressed rats	Pohorecky and Roberts, 1991
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Long−Evans rats	3 mg/kg	i.p. in 2 ml/kg	+		McNamara and Skelton, 1992
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	1 and 2 mg/kg	i.p., 1 ml/kg	0	at 2 mg/kg, walking and rearing were decreased	Hughes, 1993
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	5 mg/kg/day	i.p., for 14 and 28 days	+	chronic treatment	Sherif and Oreland, 1994
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague−Dawley rats	100 ng	bilaterally infused in the midbrain central gray	+	ovariectomized estradiol benzoate-treated rats	McCarthy et al., 1995
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	rats	10 mg/kg	i.p., given from days 13 to 20 of gestation	−	chronic treatment	Singh et al., 1996
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	2.5−5 mg/kg	i.p., 5 ml/kg	+		Rex et al., 1996

(continued on next page)

Table 1 (*continued*)

Drug	Mechanisms	Animals	Doses	Routes	Effects	Comments	Reference
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.05–1 mg/kg	i.p.	+		Nazar et al., 1997
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	chicks (Cobb Harding)	0.05, 0.1 or 0.2 mg/kg	i.p.	0		Marin et al., 1997
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	chicks (Cobb Harding)	0.5 or 1 mg/kg	i.p.	−	sedation	Marin et al., 1997
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley rats	1st hour: 1 mg/kg 2nd hour: 3 mg/kg	i.p.	0	sedation	Broderick et al., 1998
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Charles Foster albino rats	0.25 mg/kg	i.p.	−	streptozotocin-induced diabetic rats	Ramanathan et al., 1998
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Charles Foster albino rats	1 mg/kg	i.p.	+	streptozotocin-induced diabetic rats	Ramanathan et al., 1998
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Charles Foster albino rats	0.25–1 mg/kg	i.p.	+	non-diabetic rats	Ramanathan et al., 1998
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley–Hsd rats	2 and 5 mg/kg	i.p., in 2 ml	+		Schmitt and Hiemke, 1998
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	PVG/OlaHsd	2 and 5 mg/kg	i.p., in 2 ml	+		Schmitt and Hiemke, 1998
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.5, 1.25, 2.5 and 5 mg/kg	i.p.	+ (except at 5 mg/kg)	bilateral electrical stimulation in the medial prefrontal cortex	Nakamura-Palacios et al., 1999
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	PVG/OlaHsd rats	1.5 mg/kg	i.p.	+		Schmitt et al., 2000
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.05, 0.2, 1.5 mg/kg	i.p.	0	decrease motor activity	Siemiatkowski et al., 2000
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	pig (Landrace × Yorkshire)	0.8 mg/kg	im	0		Andersen et al., 2000
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	mice	2 mg/kg/day	during 14 days	+	−no stimulant effect on locomotion −chronic treatment	Boerngen-Lacerda and Souza-Formigoni, 2000
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	CF1 mice	1.5 mg/kg	i.p.	+	alterations in sit and groom	Choleris et al., 2001

Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley rats	400 μg/kg	i.p.	0	decrease activity (square crossing)	Tashma et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.03–10 mg/kg	i.p.	0	aged rats (24 months old)	Wikinski et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Fischer 344 rats	0.5–4 mg/kg	i.p.	+		Bert et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Harlan–Wistar rats	0.5–4 mg/kg	i.p.	+		Bert et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	2 mg/kg	i.p.		increased motor activity	Beaufour et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats, male	1.5 mg/kg	s.c., over gestation days 14–20	+	–non-handled (NH) –chronic treatment	Cannizzaro et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats, female	1.5 mg/kg	s.c., over gestation days 14–20	–	–non-handled (NH) –chronic treatment	Cannizzaro et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats, male and female	1.5 mg/kg	s.c., over gestation days 14–20	Slightly influenced	–short-lasting handled (SLH) –chronic treatment	Cannizzaro et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats, male	1.5 mg/kg	s.c., over gestation days 14–20	+	–long-lasting handled (LLH) –chronic treatment	Cannizzaro et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats, female	1.5 mg/kg	s.c., over gestation days 14–20	+	–long-lasting handled (LLH) –chronic treatment	Cannizzaro et al., 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Broiler chick (Cobb Harding hybrid)	0.05 mg/kg	i.p.	0	low latency to peck pebbles	Salvatierra and Arce, 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Broiler chick (Cobb Harding hybrid)	0.05 mg/kg	i.p.	+	moderate latency to peck pebbles	Salvatierra and Arce, 2001
Diazepam	Benzodiazepine, benzodiazepine receptor full agonist	Broiler chick (Cobb Harding hybrid)	0.05 mg/kg	i.p.	+	high latency to peck pebbles	Salvatierra and Arce, 2001
Doramectin	$GABA_A$ receptor agonist	Wistar rats	100, 300 and 1000 μg/kg	s.c.	0	–few alterations in locomotion frequency –reduction of grooming	De Souza Spinosa et al., 2000
Estazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist	Wistar rats	0.5–1 mg/kg	p.o.	+		Ueki et al., 1984
Estazolam	Triazolobenzodiazepine, benzodiazepine receptor agonist	Wistar rats	10 mg/kg	p.o.	0		Ueki et al., 1984

(continued on next page)

Table 1 (*continued*)

Drug	Mechanisms	Animals	Doses	Routes	Effects	Comments	Reference
Ethanolamine *O*-sulfate (EOS)	GABA-Transaminase inhibitor	inbred rats	200 and 400 μg	intracisternal	0	decreased activity	Nobrega and Coscina, 1983
EOS	GABA-Transaminase inhibitor	inbred strains rats	100 followed by 0 followed by 200 μg in 20 μl deionized water	intracisternal injection in the lateral hypothalamus, 1 week separating each injection	0	decreased activity	Coscina and Nobrega, 1989
EOS	GABA-Transaminase inhibitor	Wistar rats	200 mg/kg/day	from postnatal days 3 to 21	0	−chronic treatment −reduced activity	Taira et al., 1992
FG-7142 (*N*-methyl-β-carboline-3-carboxamide)	Benzodiazepine receptor inverse agonist	inbred strains rats	1, 5, 10, 30 mg/kg	i.p.	0	−increased ambulation −increased rearings	Bruhwyler et al., 1991
FG-7142	Benzodiazepine receptor inverse agonist	mice	20 mg/kg/day	implanted s.c. osmotic pump for 1 to 14 days	−days 1 and 2: 0 −days 4 and 7: + −day 14: −	chronic treatment	Pritchard et al., 1991
FG 7142	Benzodiazepine receptor inverse agonist	Sprague–Dawley rats, male	5,10 and 20 mg/kg	i.p., in 2 ml/kg	−		Meng and Drugan, 1993
FG 7142	Benzodiazepine receptor inverse agonist	Sprague–Dawley rats, female	40 mg/kg	i.p., in 2 ml/kg	−		Meng and Drugan, 1993
FG 7142	Benzodiazepine receptor inverse agonist	Chicks (Cobb Harding)	0.1 and 1 mg/kg	i.p., 0.2 ml/100 g	−		Marin et al., 1997
Flumazenil (Ro 15-1788)	Benzodiazepine receptor antagonist	mice	1 and 5 mg/kg/day	implanted s.c. osmotic pump for 14 days	days 1, 2 and 4: 0	chronic treatment	Miller et al., 1989a
Flumazenil	Benzodiazepine receptor antagonist	mice	2 mg/kg/day	implanted s.c. osmotic pump for 14 days	days 7 and 14: +	chronic treatment	Miller et al., 1989a
Flumazenil	Benzodiazepine receptor antagonist	RLA/Verh rats	3.5 and 6.3 mg/kg/day	from day 15 to the 14th day after birth	0	chronic treatment	Ferre et al., 1996
Flumazenil	Benzodiazepine receptor antagonist	Wistar rats	0.1–1–10 mg/kg	i.p.	0		Nazar et al., 1997
Flurazepam	Benzodiazepine, benzodiazepine receptor full agonist	NIH albino mice	1, 5, 10 and 20 mg/kg	i.p., in 5 ml/kg	+		Crawley, 1981
Flurazepam	Benzodiazepine, benzodiazepine receptor full agonist	Sprague–Dawley albino rats	5, 10 and 20 mg/kg	s.c., in 1 ml/kg	0		Britton and Britton, 1981

Girisopam: GYKI 51,189(EGIS 5810): (1-(3-chlorophenyl)-4-methyl-7, 8-dimethoxy-5H-2,3-benzodiazepine)	2,3-Benzodiazepine, benzodiazepine receptor agonist	Sprague–Dawley rats	37.5–50 mg/kg	i.p.	+		Horvath et al., 1992
GYKI 52,322 (EGIS 6775): (1-(4-aminophenyl)-4-methyl-7,8-dimethoxy-5H-2,3-benzodiazepine)	2,3-Benzodiazepine, benzodiazepine receptor agonist	Sprague–Dawley rats	2.5–5–7.5–10 mg/kg	i.p.	+		Horvath et al., 1992
Lorazepam	Benzodiazepine, benzodiazepine receptor full agonist	Lister rats	0.25 or 1.25 mg/kg	s.c., between postnatal days 7 and 21	0	chronic treatment	File and Tucker, 1983
Lorazepam	Benzodiazepine, benzodiazepine receptor full agonist	Mice, 3 weeks old	2 mg/kg/day	from days 13 to 20 of gestation	0	–prenatal injection –chronic treatment –increased activity	Chesley et al., 1991
Lorazepam	Benzodiazepine, benzodiazepine receptor full agonist	Mice, 6 weeks old	2 mg/kg/day	from days 13 to 20 of gestation	0	–prenatal injection –chronic treatment	Chesley et al., 1991
Lorazepam	Benzodiazepine, benzodiazepine receptor full agonist	inbred ICR mice	0.2–2 mg/kg	i.p.	0	Dose-dependent decreased activity	Fahey et al., 1999
Lorazepam	Benzodiazepine, benzodiazepine receptor full agonist	Mice (CD 1(ICR)BR)	2 mg/kg	pump implanted subcutaneously	0	–total distance travelled decrease –nb of rearings decrease –total stereotypies decrease	Fahey et al., 2001
Lormetazepam	Benzodiazepine, benzodiazepine receptor full agonist	inbred ICR mice	0.2–2 mg/kg	i.p.	0	Dose-dependent decreased activity	Ueki et al., 1985
Midazolam	Benzodiazepine, benzodiazepine receptor full agonist	Hooded rats	1–10 mg/kg	i.p.	0	dose dependently reduced general activity	Yerbury and Cooper, 1987
Midazolam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.01 and 0.1μg	in the hippocampus	+		Stefanski et al., 1993
Midazolam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.01 and 0.1μg	in the nucleus accumbens septi	0		Stefanski et al., 1993
Midazolam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.01–0.1–0.5–1 mg/kg	i.p.	+		Nazar et al., 1997
Midazolam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.5 μg/4μl	i.c.v.	+		Czlonkowska et al., 1999

(continued on next page)

Table 1 (*continued*)

Drug	Mechanisms	Animals	Doses	Routes	Effects	Comments	Reference
Midazolam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	0.1 μg/site	in the dentate gyrus of the dorsal hippocampus	+		Nazar et al., 1999a,b
Midazolam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	10 μg/site	in the dentate gyrus of the dorsal hippocampus	0	inhibit motor activity	Nazar et al., 1999a,b
Muscimol	$GABA_A$ receptor agonist	Wistar rats	0.2 mg/kg	between the 1st and the 21st postnatal days	0	decreased activity	Taira et al., 1993
Muscimol	$GABA_A$ receptor agonist	Wistar rats	1 m/kg	p.o.	0	rats prenatally exposed to delta9-tetrahydrocannabinol or oil	Garcia-Gil et al., 1999
Muscimol	$GABA_A$ receptor agonist	Wistar rats	0.5 and 1 μg per side	bilateral infusion into the ventral hippocampus	0	−dose-dependent −decreased activity	Bast et al., 2001b
Nitrazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	1 mg/kg	p.o.	+	slight effect	Ueki et al., 1984
Nitrazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	2 mg/kg	p.o.	+	decrease ambulation 2 and 4 h after administration	Ueki et al., 1984
Nitrazepam	Benzodiazepine, benzodiazepine receptor full agonist	Wistar rats	20 mg/kg	p.o.	+	increase ambulation 2 h after administration	Ueki et al., 1984
Oxazepam	Benzodiazepine, benzodiazepine receptor full agonist	mice	5, 15 and 50 mg/kg twice daily	p.o., from 12 to 16 of pregnancy	0	−chronic treatment −at 60 days: reduction of locomotion	Alleva et al., 1985
Oxazepam	Benzodiazepine, benzodiazepine receptor full agonist	mice	5, 15 and 50 mg/kg twice daily	p.o., from 12 to 16 of pregnancy	0	−chronic treatment −at 14−16 days: reduced activity	Alleva et al., 1985
Oxazepam	Benzodiazepine, benzodiazepine receptor full agonist	CD-1 mice	15 mg/kg	p.o., twice a day, on days 12−16 of fetal life	0	chronic treatment	Laviola et al., 1992
Oxazepam	Benzodiazepine, benzodiazepine receptor full agonist	CD-1 mice	15 mg/kg	p.o., twice a day, on days 12−16 of fetal life	0	−chronic treatment −increase frequency of grooming, rearing, sniffing −reduced walking	Fiore et al., 1995
Pentabarbitol	Barbiturate agonist	Mongolian gerbils (*Meriones unguiculatus*)	15 and 20 mg/kg	i.p., 0.34 ml per gerbil	+		Jarbe and Johansson, 1977

Pentabarbitol	Barbiturate agonist	Sprague–Dawley albino rats	5 and 10 mg/kg	s.c., in 1 ml/kg	+	single food pellet in the center of a new open field environment	Britton and Britton, 1981
Pentabarbitol	Barbiturate agonist	NIH albino mice	40 mg/kg	i.p., in 5 ml/kg	+		Crawley, 1981
Phenazepam	Benzodiazepine, benzodiazepine receptor agonist	C57BL/6 mice	0.05, 0.075, 0.1 mg/kg	i.p.	–	Dose-dependent suppression of locomotor activity	Seredenin et al., 1990
Phenazepam	Benzodiazepine, benzodiazepine receptor agonist	BALB/c mice	0.05 mg/kg	i.p.	+		Seredenin et al., 1990
Phenazepam	Benzodiazepine, benzodiazepine receptor agonist	BALB/c mice	0.075–0.1 mg/kg	i.p.	0		Seredenin et al., 1990
Phenazepam	Benzodiazepine, benzodiazepine receptor agonist	F1 (C57BL/6 × BALB/c) mice	0.05 mg/kg	i.p.	0	Dose-dependent suppression of locomotor activity	Seredenin et al., 1990
Phenazepam	Benzodiazepine, benzodiazepine receptor agonist	F1 (C57BL/6 × BALB/c) mice	0.075, 0.1 mg/kg	i.p.	–	Dose-dependent suppression of locomotor activity	Seredenin et al., 1990
Phenobarbitol	Barbiturate agonist	Wistar rats, male	10 and 20 mg/kg	s.c., from days 5 to 45 of life; 0.03–0.05 ml from days 5 to 25 and 0.06–0.1 ml from days 26 to 45	+ (decreased defecation)	–chronic treatment –increased ambulation	Fonseca et al., 1976
Phenobarbitol	Barbiturate agonist	Wistar rats, female	10 and 20 mg/kg	s.c., from days 5 to 45 of life; 0.03–0.05 ml from days 5 to 25 and 0.06–0.1 ml from days 26 to 45	+ (increased defecation)	–chronic treatment –decreased ambulation	Fonseca et al., 1976
Picrotoxin	Picrotoxin and *t*-butylbicyclophosphorothionate binding site on $GABA_A$ receptor pentamert	inbred strain rats	25 and 50 ng in 0.25 μl	in the midbrain periaqueductal gray matter	0	–increased backward locomotion –decreased grooming	Depaulis and Vergnes, 1986
Picrotoxin	Picrotoxin and *t*-butylbicyclophosphorothionate binding site on $GABA_A$ receptor pentamert	Sprague–Dawley rats	0.5–1 mg/kg	i.p. in 2 ml/kg	0		Fernandez-Teruel et al., 1990
Picrotoxin	Picrotoxin and *t*-butylbicyclophosphorothionate binding site on $GABA_A$ receptor pentamert	Wistar rats	0.75 mg/kg	s.c., on day 18 of pregnancy and daily during the first 5 days of lactation	0	–chronic treatment –hyperactivity	Silva et al., 1995

(continued on next page)

Table 1 (*continued*)

Drug	Mechanisms	Animals	Doses	Routes	Effects	Comments	Reference
Picrotoxin	Picrotoxin and *t*-butylbicyclophosphorothionate binding site on $GABA_A$ receptor pentamer	Wistar rats	0.1 μg/site	in the dentate gyrus of the dorsal hippocampus	+		Nazar et al., 1999a,b
Picrotoxin	Picrotoxin and *t*-butylbicyclophosphorothionate binding site on $GABA_A$ receptor pentamer	Wistar rats	150 ng/0.5 μl per side	bilateral infusions into the ventral hippocampus	+		Bast et al., 2001a
Piracetam	GABA derivative compound	Wistar rats	250 and 500 mg/kg	p.o., for 7 and 14 days	+	chronic treatment	Bhattacharya et al., 1993
Piracetam	GABA derivative compound	Wistar rats	250 and 500 mg/kg	p.o.	0		Bhattacharya et al., 1993
3α-hydroxy-5α-pregna-20-one (3α, 5α THP)	Neurosteroid binding to $GABA_A$ receptor pentamer	mice	1 or 2 μg	i.c.v.	0		Khisti et al., 2000
3α, 5α THP	Neurosteroid binding to $GABA_A$ receptor pentamer	mice	0.5, 1, 2 mg/kg	i.p.	0		Khisti et al., 2000
5α-pregnan-3α-ol-20-one (THP)	Neurosteroid binding to $GABA_A$ receptor pentamer	Long–Evans rats	3.2 or 6.4 mg/kg	s.c.	0		Frye and Sturgis, 1995
5α-THDOC (3α-21-dihydroxy-5α-pregnanolone or α-tetrahydrodeoxycorticosterone)	Neurosteroid binding to $GABA_A$ receptor pentamer	Wistar rats	10 and 20 μg/4μl	i.c.v.	–		Czlonkowska et al., 1999
5β-THDOC (3α-21-dihydroxy-5β-pregnanolone, 5βtetrahydrodeoxycorticosterone)	Neurosteroid binding to $GABA_A$ receptor pentamer	Wistar rats	5 and 10 μg/4μl	i.c.v.	–		Czlonkowska et al., 1999
5α-pregnan-3α-ol-11,20-dione	Neurosteroid binding to $GABA_A$ receptor pentamer	Long–Evans rats	3.2 or 6.4 mg/kg	s.c.	0		Frye and Sturgis, 1995
4-pregnen-3, 20-dione-17α-hydroxyprogesterone	Neurosteroid binding to $GABA_A$ receptor pentamer	Long–Evans rats	3.2 or 6.4 mg/kg	s.c.	0		Frye and Sturgis, 1995
5-pregnen-3β-ol-20-one sulfate	Neurosteroid binding to $GABA_A$ receptor pentamer	Long–Evans rats	3.2 or 6.4 mg/kg	s.c.	0		Frye and Sturgis, 1995
pregnenolone sulfate (PS)	Neurosteroid binding to $GABA_A$ receptor pentamer	Wistar rats	5 mg/kg	s.c.	0		Reddy et al., 1998
PS	Neurosteroid binding to $GABA_A$ receptor pentamer	Wistar rats	5, 10 and 20 μg/4μl	i.c.v.	+	Dose-dependent	Czlonkowska et al., 1999

Progesterone	Neurosteroid binding to $GABA_A$ receptor pentamer	inbred strains mice	10 mg/kg	s.c.	0		Reddy et al., 1998
R05-4864	Peripheric benzodiazepine receptor ligand	NIH albino mice	20 mg/kg	i.p., in 5 ml/kg	0		Crawley, 1981
Ro 11-6893	1,4-Benzodiazepine, Ro 11-6896, inactive stereoisomer of Ro 11-6896	Mongolian gerbils (*Meriones unguiculatus*)	10 mg/kg	i.p., 2 injections of 4 ml/kg	0		Hiltunen and Jarbe, 1986
Ro 11-6896	1,4-Benzodiazepine, Benzodiazepine receptor agonist	Mongolian gerbils (*Meriones unguiculatus*)	1 mg/kg	i.p., 2 injections of 4 ml/kg	0		Hiltunen and Jarbe, 1986
Ro 15-4513	Benzodiazepine receptor inverse agonist	Charles River rats	2.5 mg/kg	i.p.	0		June and Lewis, 1989
Ro 15-4513	Benzodiazepine receptor inverse agonist	inbred strains rats	1.25 and 2.5 mg/kg	i.p.	0		June et al., 1989
Ro 17-1812	Benzodiazepine receptor partial agonist	Hooded rats	1–10 mg/kg	i.p.	0	decreased grooming at high dose	Yerbury and Cooper, 1987
Ro 19-8022	Benzodiazepine receptor partial agonist	Wistar rats	0.1–0.5–1–10 mg/kg	i.p.	0		Nazar et al., 1997
RY 008	Benzodiazepine receptor partial inverse agonist	Wistar rats	50 and 500 ng	intrastriatal injection	0		June et al., 1998
SKF 89976-A	GABA uptake inhibitor	PVG/OlaHsd rats	5–10–15–20–25 mg/kg	i.p., injected in 2.5 ml	+		Schmitt and Hiemke, 1999
SKF-89976-A	GABA uptake inhibitor	PVG/OlaHsd rats	15 mg/kg	i.p.	+		Schmitt et al., 2001
SR 95531	$GABA_A$ receptor antagonist	Wistar rats	50 ng	intrastriatal injection	0		June et al., 1998
Testosterone	Neurosteroid binding to $GABA_A$ receptor pentamer	Wistar rats (immature, 6 weeks old)	40 μg/100 g body weight	i.p., once daily for 3 consecutive days	0	–observed at 4 and at 24 h after injection –inhibit horizontal and vertical locomotor activity	Lambadjieva, 1998
Testosterone	Neurosteroid binding to $GABA_A$ receptor pentamer	Wistar rats (immature, 6 weeks old)	40 μg/100 g body weight	i.p., once daily for 3 consecutive days	0	–continual light leads –observed at 4 and 24 h after injection –increased horizontal and vertical locomotor activity	Lambadjieva, 1999
THBC (1,2,3,4-tetrahydro-β-carboline)	Benzodiazepine receptor inverse agonist	inbred strains rats	10 or 50 ng in 3 μl	bilaterally into the hippocampus	0	reduced motor activity	Huttunen and Myers, 1986
THBC (1,2,3,4-tetrahydro-β-carboline)	Benzodiazepine receptor inverse agonist	inbred strains rats	50 ng in 3 μl	bilaterally into the hippocampus	+ (increase time of freezing-immobilisation)		Huttunen and Myers, 1986
THIP (4,5,6,7-tetrahydroxi-azolo-5,4*c*-pyridine-3-ol)	$GABA_A$ receptor agonist	inbred strain rats	20 mg/kg	s.c.	0	depressant effect	Borsini et al., 1988

(continued on next page)

Table 1 (*continued*)

Drug	Mechanisms	Animals	Doses	Routes	Effects	Comments	Reference
THIP	$GABA_A$ receptor agonist	Wistar rats	0.5–0.75–1 mg/kg	route?	0	decrease frequency of grooming	Barros et al., 1994
Tiagabine	GABA uptake inhibitor	rats	18.5 mg/kg	i.p.	+		Schmitt and Hiemke, 1999
Tiagabine	GABA uptake inhibitor	PVG/OlaHsd rats	4.5 mg/kg	i.p.	0		Schmitt. et al., 2000
Tiagabine	GABA uptake inhibitor	PVG/OlaHsd rats	18.5 mg/kg	i.p.	+		Schmitt et al., 2000
Triazolam	Triazolobenzodiazepine, Benzodiazepine receptor agonist	Mice CD1	0.02–0.05 mg/kg	i.p.	−	dose-dependent fashion	Lopez et al., 1988
Vigabatrin	GABA-Transaminase inhibitor	Wistar rats	50 mg/kg	i.p.	+	observed 2,4 and 24 h after injection	Sherif and Oreland, 1994
Vigabatrin	GABA-Transaminase inhibitor	Wistar rats	50 mg/kg/day	i.p., for 14 and 28 days	0	chronic treatment	Sherif and Oreland, 1994
Vigabatrin	GABA-Transaminase inhibitor	Wistar rats	250 mg/kg	i.p.	+	isolated rats	Sherif and Oreland, 1995
Vigabatrin	GABA-Transaminase inhibitor	Wistar rats	250 mg/kg	i.p.	0	socially housed rats	Sherif and Oreland, 1995
Zolpidem	Selective Benzodiazepine receptor α1 receptor partial agonist	Wistar rats	0.3–3 mg/kg	i.p., 2 ml/kg	0	decrease locomotion	Sanger and Zivkovic, 1988
Zolpidem	Selective Benzodiazepine receptor α1 receptor partial agonist	Wistar rats	0.005–0.001–0.1–1 mg/kg	i.p.	0		Nazar et al., 1997
Zolpidem	Selective Benzodiazepine receptor α1 receptor partial agonist	PVG/OlaHsd and Sprague–Dawley–Hsd rats	0.05 mg/kg	i.p.	+		Schmitt and Hiemke, 1998
Zolpidem	Selective Benzodiazepine receptor α1 receptor partial agonist	PVG/OlaHsd and Sprague–Dawley–Hsd rats	3 mg/kg	i.p.	0	decrease activity	Schmitt and Hiemke, 1998
Zolpidem	Selective Benzodiazepine receptor α1 receptor partial agonist	Wistar rats	10 μg/site	in the dentate gyrus of the dorsal hippocampus	−	decrease motor activity	Nazar et al., 1999a,b
Zolpidem	Selective Benzodiazepine receptor α1 receptor partial agonist	Wistar rats	0.1 mg/kg	i.p.	−		Siemiatkowski et al., 2000
Zolpidem	Selective Benzodiazepine receptor α1 receptor partial agonist	Wistar rats	2 mg/kg	i.p.	−		Siemiatkowski et al., 2000
Zolpidem	Selective Benzodiazepine receptor α1 receptor partial agonist	PVG/OlaHsd rats	0.05 mg/kg	i.p., in 2.5 ml	0		Schmitt et al., 2000
Zopiclone	Cyclopyrrolone derivative, $GABA_A$ receptor complex modulator	ddY mice	20 mg/kg	p.o.	0	decrease of activity and rearing at high doses	Ueki, 1987

+, Anxiolytic-like effect; −, anxiogenic-like effect; 0, no anxiolytic or anxiogenic-like effects (in some cases, non-specific effects can be observed but this is specified in the "comment" column); i.p., intraperitoneal; p.o., per os; s.c., subcutaneous; i.c.v., intracerebroventricular.

open field may provide a good measure of the approach response toward novelty, that is, exploration.

The open field has become so popular that its use has been extended to a great number of species, including calves, pigs, lambs, rabbits, pullets, primates, bush babies, honeybees and lobsters. In fact, it has become a convenient procedure to measure not only anxiety-like behaviors, but also sedation or activity. In fact, anxiety behavior in the open field is triggered by two factors: individual testing (the animal is separated from its social group) and agoraphobia (as the arena is very large relative to the animal's breeding or natural environment). It is clear that these two factors may trigger anxiety behavior only in gregarious species and/or in species that show fear of open spaces into which they are forced. This is precisely the case with rodents that live in social groups and in small tunnels. This is of course not the case in species such as lambs or cows that live in large fields. For these reasons, in experiments involving rodents, observers are not measuring the effects of treatments on exploration, as is sometimes claimed, but the effects on the reaction of the subjects to a stressful event. Therefore, anxiolytic treatments do not themselves increase exploration in the open field but they decrease the stress-induced inhibition of exploration behavior.

Behavior of rodents in the open field depends mainly on the tactile sensory factors. Indeed, mice without vibrissae no longer show thigmotaxic behavior, as they lose tactile contact with the walls (unpublished data). They therefore display an increased percent of entries in the central area, which could be interpreted as anxiolytic-like behavior. One must thus emphasize the possibility of misinterpretation of data related to effects of some treatments on the sensory characteristics of the animals. It should also be noted that exploration can be increased by some factors such as food or water deprivation: it is therefore very important to verify that a given treatment does not act on such variables, before concluding about possible effects on anxiety-like behaviors. Finally, open field behavior also depends on lighting conditions and the light–dark cycle, so that it may be relevant to ensure that a treatment does not modify internal clock-related behaviors and to test the treatment under different lighting conditions.

The effects of many different drugs have been investigated in the open field, including compounds with effective or potential anxiolytic effects (benzodiazepines, serotonin ligands, neuropeptides) but also compounds with stimulant (amphetamine, cocaine), sedative (neuroleptic) or prostration-inducing (epileptogenic drugs) activity. An increase in central locomotion or in time spent in the central part of the device without modification of total locomotion and of vertical exploration can be interpreted as an anxiolytic-like effect while the contrary, that is a decrease of these variables, is associated with anxiogenic effects. Increased locomotion can be considered a stimulant effect while decreased vertical activity and locomotion are related to sedation or to post-ictal prostration. It should be said here that the decrease in vertical exploration appears at lower doses than does the decrease in rearing, so that this variable can be considered a more sensitive one. In this paper, we will focus on the effects of pharmacological treatment on anxiety measures in the open field and not on their sedative or stimulant effects. Therefore, this is not a general review on drugs in the open field, but a review of the effects of drugs on anxiety-like variables in the open field. The action of three classes of pharmacological compounds will be reviewed: the effects of compounds acting on the $GABA_A$ pentamer (mainly benzodiazepine receptor ligands but also $GABA_A$ receptor, barbiturate and neurosteroid ligands), the effects of drug acting like 5-hydroxytryptamine (5-HT) (ligands of the different 5-HT receptors as well as selective serotonin reuptake inhibitors, neurotoxins of 5-HT, etc.) and the effects of neuropeptidergic ligands (corticotropin releasing factor: CRF, cholecystokinin: CCK, neurokinin: NK, neuropeptide Y, etc).

2. Effects of compounds acting on the $GABA_A$ pentamer

Classical benzodiazepines are widely used for the clinical treatment of anxiety. They act via the benzodiazepine receptors which are present on the $GABA_A$ pentameric complex. The $GABA_A$ receptors can be allosterically modulated by compounds binding to at least six different sites: the benzodiazepine receptors, a binding site for barbiturates, a site for neurosteroids, a site for the convulsant drugs, picrotoxin and *t*-butylbicyclophosphorothionate, one for flurosemide and one for loreclezole (see Belzung et al., 2002 for more details). In the clinic, benzodiazepine receptor agonists and barbiturate receptor agonists have been shown to display an anxiolytic action while no such effects were seen with other ligands of the pentamer, including $GABA_A$ receptor agonists. The effects of compounds binding on different parts of the $GABA_A$ pentamer in animals subjected to the open field are summarized in Table 1.

Acute administration of benzodiazepine receptor full agonists mostly induces anxiolytic-like effects as they elicit an increase of the percent of entries in the central part of the open field (56% of the studies). However, in some case, these drugs also have no effects (31% of the studies) or even anxiogenic effects (13%). Chronic injection of these compounds mostly does not elicit any effect (66% of the studies). The most used compound is diazepam (52% of the studies investigating the action of a benzodiazepine full agonist). This range of effects (from anxiolytic-like to anxiogenic-like) may be related to the dose used (high doses induce non-specific sedative effects) and also to subtle differences in species or in procedures. For example, moderate doses of benzodiazepines are known to decrease activity in rats and to increase it in mice; this can lead to non-specific modifications in the number of entries in the central part of the apparatus. To avoid this it may be useful to calculate the percent of central entries, rather than the number of entries per se. Some species seem inappropriate for the assessment of anxiolytic effects in the open field: for

Table 2
Effects of ligand acting upon serotonergic neurotransmission on animals subjected to the open field test

Drug	Mechanism	Animals	Doses	Routes	Effects	Comments	Reference
(−)Pindolol	Non-selective antagonist	Sprague–Dawley rats (200–250 g)	10	i.p.	+	Locomotion increased	Lucki et al., 1989
5,7-DHT	5-HT neurotoxin	CFHB rats (270–300 g)	5 μg	Fornix, 16–20 days	–		Williams et al., 1990
5,7-DHT	5-HT neurotoxin	Wistar rats (180–200 g)	250 μg/10 μl	i.c.v., 1 week before	0		Nazar et al., 1999b
5,7-DHT + Zolpidem (0,1 mg)	5-HT neurotoxin	Wistar rats (180–200 g)	250 μg/10 μl	i.c.v., 1 week before	0	No interaction	Nazar et al., 1999b
5-CT	Non-selective agonist	Lister rats (200–250 g)	1–10 nmol	DPAG	–		Beckett et al., 1992
5-HT	Endogenous ligand	Rats (180–220 g)	10 μg	Nucleus accumbens	–		Plaznik et al., 1991
5-HTP	5-HT precursor	Swiss mice (20–25 g)	50–250	i.p.	0		Wong and Ong, 2001
5-HTP + PCPA (360 mg/kg)	5-HT precursor	Swiss mice (20–25 g)	250	i.p.	+	The combination yielded anxiolytic-like activity	Wong and Ong, 2001
8-OH-DPAT	5-HT_{1A} full agonist	Lister rats (200–250 g)	3–25 nmol	DPAG	–		Beckett et al., 1992
8-OH-DPAT	5-HT_{1A} full agonist	Sprague–Dawley rats (280–320 g)	0.025–0.4	s.c.	–		Ahlenius et al., 1991
8-OH-DPAT	5-HT_{1A} full agonist	Rats (180–220 g)	50–20 μg	Nucleus accumbens	–		Plaznik et al., 1991
8-OH-DPAT	5-HT_{1A} full agonist	CD-COBS rats (200–300 g)	0.125–0.5	s.c.	0	Non-stressed rats	Carli et al., 1989
8-OH-DPAT	5-HT_{1A} full agonist	Wistar rats (180–220 g)	0.0001–0.005	Nucleus accumbens	0		Stefanski et al., 1993
8-OH-DPAT	5-HT_{1A} full agonist	CD-COBS rats (200–300 g)	0.125–0.5	s.c.	+	Stressed rats	Carli et al., 1989
8-OH-DPAT	5-HT_{1A} full agonist	Sprague–Dawley rats (200–250 g)	2.5–5	i.p.	+	Locomotion increased	Lucki et al., 1989
8-OH-DPAT	5-HT_{1A} full agonist	Rats		Hippocampus	+		Plaznik et al., 1991
8-OH-DPAT	5-HT_{1A} full agonist	Wistar rats (180–220 g)	0.025–0.1	i.p.	+	65 dB noise	Stefanski et al., 1992
8-OH-DPAT	5-HT_{1A} full agonist	CD-COBS rats (200–250 g)	0.005	Hippocampus	+		Carli et al., 1993
8-OH-DPAT	5-HT_{1A} full agonist	Wistar rats (180–220 g)	0.0001–0.001	Hippocampus	+		Stefanski et al., 1993
8-OH-DPAT	5-HT_{1A} full agonist	Wistar rats (180–220 g)	0.0005	Hippocampus	+	+5,7-DHT	Stefanski et al., 1993
8-OH-DPAT	5-HT_{1A} full agonist	Wistar rats (175–225 g)	0.03	i.p.	+	Latency to eat in the open field was reduced	Rex et al., 1998
8-OH-DPAT	5-HT_{1A} full agonist	Male and female C57BL6/J×129/sv mice	0.1–1	?	0		Ramboz et al., 1998
Amitriptyline	5-HT reuptake inhibitor	AB mice (4–6 weeks)	5	4 weeks in drinking water	–	Low active mice	Jähkel et al., 1994
Amitriptyline	5-HT reuptake inhibitor	AB mice (4–6 weeks)	5	4 weeks in drinking water	0	High active mice	Jähkel et al., 1994
Amitriptyline	5-HT reuptake inhibitor	Sprague–Dawley rats (325–375 g)	10	i.p., for 21 days (x1)	0		Mar et al., 2000
Amitriptyline	5-HT reuptake inhibitor	Olfactory bulbectomized Sprague–Dawley rats (325–375 g)	10	i.p., for 21 days (x1)	0		Mar et al., 2000
Buspirone	5-HT_{1A} partial agonist	Sprague–Dawley rats (330–420 g)	0.04–10	i.p.	–	15W	Panickar and McNaughton, 1991
Buspirone	5-HT_{1A} partial agonist	Rats (180–220 g)	0.1–5 μg	Nucleus accumbens	–		Plaznik et al., 1991
Buspirone	5-HT_{1A} partial agonist	CD-COBS rats (200–300 g)	0.1–1	s.c.	0	Non-stressed rats	Carli et al., 1989

Buspirone	5-HT_{1A} partial agonist	Wistar rats (180–220 g)	0.0001–0.005	Nucleus accumbens,	0		Stefanski et al., 1993
Buspirone	5-HT_{1A} partial agonist	CD-COBS rats (200–300 g)	0.1–1	s.c.	+	Stressed rats	Carli et al., 1989
Buspirone	5-HT_{1A} partial agonist	Rats		Hippocampus	+		Plaznik et al., 1991
Buspirone	5-HT_{1A} partial agonist	SPRD rats (200 g)	0.62	i.p.	+		Horvath et al., 1992
Buspirone	5-HT_{1A} partial agonist	Wistar rats (180–220 g)	0.3–2.5	i.p.	+	65 dB noise	Stefanski et al., 1992
Buspirone	5-HT_{1A} partial agonist	Rats	0.62–2.5		+		Stefanski et al., 1992
Buspirone	5-HT_{1A} partial agonist	Male and female Wistar rats (180 days)	1.25–2.5	i.p.	+	Sedation?	Hughes, 1993
Buspirone	5-HT_{1A} partial agonist	Wistar rats (180–220 g)	0.0025–0.005	Hippocampus	+		Stefanski et al., 1993
Buspirone	5-HT_{1A} partial agonist	Sprague–Dawley rats (350–650 g)	5	i.p., 5 daily injections	+	Animals were tested on 5 consecutive days	Angrini et al., 1998
Buspirone	5-HT_{1A} partial agonist	Male and female C57BL6/J ×129/sv mice	0.05–2.5		0		Ramboz et al., 1998
Buspirone	5-HT_{1A} partial agonist	Wistar rats (180–220 g)	0.3–2.4	i.p.	+	The drug was active on Day 1 and 24 h later after retesting	Siemiatkowski et al., 2000
Buspirone	5-HT_{1A} partial agonist	Sprague–Dawley rats (325–375 g)	3	i.p., for 21 days (x1)	0		Mar et al., 2000
Buspirone	5-HT_{1A} partial agonist	Olfactory bulbectomized Sprague–Dawley rats (325–375 g)	3	i.p., for 21 days (x1)	0		Mar et al., 2000
Citalopram	5-HT reuptake inhibitor	Female Wistar rats (250–350 g)	10–15	i.p.	–		Matto and Allikmets, 1999
Clomipramine	5-HT reuptake inhibitor	AB mice (4–6 weeks)	5	4 weeks in drinking water	0	Low active mice	Jähkel et al., 1994
Clomipramine	5-HT reuptake inhibitor	AB mice (4–6 weeks)	5	4 weeks in drinking water	0	High active mice	Jähkel et al., 1994
Clozapine	Non-selective 5-HT_{2A2C} antagonist	Wistar rats (175–225 g)	1–3	i.p.	+	Latency to eat in the open field was reduced	Rex et al., 1998
Cyanopindolol	Non-selective antagonist	Rats (180–220 g)	0.5 μg	Nucleus accumbens	–		Plaznik et al., 1991
DAU 6215	5-HT_3 antagonist	Crl. CD rats (175–220 g)	0.01–10	p.o.	0		Rizzi et al., 1993
D-Fenfluramine	5-HT stimulant	Female Fischer 344 rats (4 month)	0.6	p.o., for 30–38 days	0		Handa et al., 1996
D-Fenfluramine	5-HT stimulant	Female Fischer 344 rats (21 month)	0.6	p.o., for 30–38 days	0		Handa et al., 1996
Eltoprazine	Non-selective ligand	CD-1 mice (21.1–41.1 g)	1–4	i.p.	+		Kemble et al., 1991
Flesinoxan	5-HT_{1A} full agonist	Sprague–Dawley rats (280–320 g)	0.2–3.2	s.c.	–		Ahlenius et al., 1991
Fluoxetine	5-HT reuptake inhibitor	Female CD1 mice (22–24 g)	5	i.p.	+		De Angelis, 1996
Fluoxetine	5-HT reuptake inhibitor	SHR rats (4–5 weeks old)	5–10	i.p., once a day for 21 days	0	Washout period of 48–51 h	Durand et al., 1999
Fluoxetine	5-HT reuptake inhibitor	Wistar–Kyoto rats (4–5 weeks old)	5–10	i.p., once a day for 21 days	0	Washout period of 48–51 h	Durand et al., 1999
Fluoxetine	5-HT reuptake inhibitor	Sprague–Dawley rats (325–375 g)	10	i.p., for 21 days (x1)	0		Mar et al., 2000
Fluoxetine	5-HT reuptake inhibitor	Olfactory bulbectomized Sprague–Dawley rats (325–375 g)	10	i.p., for 21 days (x1)	0		Mar et al., 2000
Fluoxetine	5-HT reuptake inhibitor	SHR rats (4–5 weeks old)	10	p.o., for 21 days (x1)	0		Durand et al., 2000

(continued on next page)

Table 2 (*continued*)

Drug	Mechanism	Animals	Doses	Routes	Effects	Comments	Reference
Fluoxetine	5-HT reuptake inhibitor	WKY rats (4–5 weeks old)	10	p.o., for 21 days (x1)	0		Durand et al., 2000
Gepirone	5-HT_{1A} partial agonist	Sprague–Dawley rats (441 g)	2.3–4.6	i.p.	–		Knapp et al., 1992
Gepirone	5-HT_{1A} partial agonist	Wistar rats (180–220 g)	0.16–0.62	i.p.	+	65 dB noise	Stefanski et al., 1992
Gepirone	5-HT_{1A} partial agonist	Rats	0.3–0.62		+		Stefanski et al., 1992
Imipramine	NA/5-HT reuptake inhibitor	Female Long–Evans rats (12 weeks)	20	i.p.	–	Saline injection between 6 to 21 days postnatal	Dwyer and Roy, 1993
Imipramine	NA/5-HT reuptake inhibitor	Female Long–Evans rats (12 weeks)	20	i.p., for 11 days (x1)	–	Saline injection between 6 to 21 days postnatal	Dwyer and Roy, 1993
Imipramine	NA/5-HT reuptake inhibitor	Female Long–Evans rats (12 weeks)	20	i.p.	0	No saline injection	Dwyer and Roy, 1993
Imipramine	NA/5-HT reuptake inhibitor	Female Long–Evans rats (12 weeks)	20	i.p., for 11 days (x1)	0	No saline injection	Dwyer and Roy, 1993
Imipramine	5-HT/NA reuptake inhibitor	Female CD1 mice (22–24 g)	10–40	i.p.	0		De Angelis, 1996
Imipramine	5-HT/NA reuptake inhibitor	SHR rats (4–5 weeks old)	10	p.o., for 21 days (x1)	0		Durand et al., 2000
Imipramine	5-HT/NA reuptake inhibitor	WKY rats (4–5 weeks old)	10	p.o., for 21 days (x1)	0		Durand et al., 2000
Ipsapirone	5-HT_{1A} partial agonist	Wistar rats (180–220 g)	0.31–1.25	i.p.	+	65 dB noise	Stefanski et al., 1992
Ipsapirone	5-HT_{1A} partial agonist	Rats	0.3–0.62	?	+		Stefanski et al., 1992
Ipsapirone	5-HT_{1A} partial agonist	Wistar rats (175–225 g)	2	i.p.	+	Latency to eat in the open field was reduced	Rex et al., 1998
Isatin	5-HT stimulant	Wistar mice (25–30 g)	20	i.p.	–		Bhattacharya et al., 1991
Ketanserin	5-HT_2 antagonist	Sprague–Dawley rats (200–250 g)	10	i.p.	0		Lucki et al., 1989
mCPP	$5\text{-HT}_{2C/2B}$ agonist	Wistar rats (200–250 g)	1–5	i.p.	–	Sedation?	Klodzinska et al., 1989
mCPP	$5\text{-HT}_{2C/2B}$ agonist	Sprague–Dawley rats (200–250 g)	2.5–5	i.p.	–	Locomotion decreased	Lucki et al., 1989
mCPP	$5\text{-HT}_{2C/2B}$ agonist	Wistar rats (200–220 g)	0.125–1	i.v.	–		Meert et al., 1997
mCPP	$5\text{-HT}_{2C/2B}$ agonist	Wistar rats (200–220 g)	0.63–10	i.p	–		Meert et al., 1997
mCPP	$5\text{-HT}_{2C/2B}$ agonist	Wistar rats (200–220 g)	2.5–10	s.c.	–		Meert et al., 1997
mCPP	$5\text{-HT}_{2C/2B}$ agonist	Wistar rats (175–225 g)	0.1–3	i.p.	0	Latency to eat in the open field was not modified	Rex et al., 1998
MDMA	5-HT releaser	Charles Foster rats (180–220 g)	5–10	i.p.	–		Bhattacharya et al., 1998
Metergoline	Non-selective antagonist	Sprague–Dawley rats (200–250 g)	0.16–0.62	i.p.	0		Lucki et al., 1989
Methysergide	Non-selective $5\text{-HT}_{2A/2C}$ antagonist	Sprague–Dawley rats (200–250 g)	5–10	i.p.	0		Lucki et al., 1989
Methysergide	Non-selective $5\text{-HT}_{2A/2C}$ antagonist	Rats (180–220 g)	10 μg	Nucleus accumbens	0		Plaznik et al., 1991
Methysergide	Non-selective $5\text{-HT}_{2A/2C}$ antagonist	Wistar rats (200–220 g)	0.63–10	s.c.	0		Meert et al., 1997

Mianserin	5-HT_2 antagonist	Rats Sprague–Dawley (200–250 g)	2.5–5	i.p.	0		Lucki et al., 1989
Mianserin	5-HT_2 antagonist	Wistar rats (200–220 g)	0.63–10	s.c.	0		Meert et al., 1997
Mirtazapine	Non-selective 5-HT antagonist	Wistar rats (200–220 g)	10	s.c.	–		Meert et al., 1997
MK-212	Non-selective agonist	Sprague–Dawley rats (200–250 g)	0.31–0.62	i.p.	–	Locomotion decreased	Lucki et al., 1989
NDO 008	5-HT_{1A} agonist	Rats (180–220 g)	1–5 μg	Nucleus accumbens	0		Plaznik et al., 1991
Ondansetron	5-HT_3 antagonist	Wistar rats (250–270 g)	0.25–20	i.p.	0		Papp and Przegalinski, 1989
Ondansetron	5-HT_3 antagonist	Wistar rats	0.0005–0.005	Hippocampus	0		Stefanski et al., 1993
Ondansetron	5-HT_3 antagonist	Rats		Accumbens	+		Plaznik et al., 1991a
Ondansetron	5-HT_3 antagonist	Wistar rats (180–220 g)	0.1–1.5	i.p.	+	65 dB noise	Stefanski et al., 1992
Ondansetron	5-HT_3 antagonist	Rats	0.001–0.1	?	+		Stefanski et al., 1992
Ondansetron	5-HT_3 antagonist	Wistar rats	0.001–0.0025	Nucleus accumbens septi	+		Stefanski et al., 1993
Ondansetron	5-HT_3 antagonist	Wistar rats (175–225 g)	0.0003	i.p.	+	Latency to eat in the open field was reduced	Rex et al., 1998
Paroxetine	5-HT reuptake inhibitor	Wistar–Kyoto rats	10	i.p., for 10 days (x1)	0		Paré et al., 1999
Paroxetine	5-HT reuptake inhibitor	Sprague–Dawley rats	10	i.p., for 10 days (x1)	0		Paré et al., 1999
Paroxetine	5-HT reuptake inhibitor	Wistar rats	10	i.p., for 10 days (x1)	0		Paré et al., 1999
PCA	5-HT neurotoxin	Wistar rats (286–360 g)	2	i.p., 21 days	0		Harro et al., 2001
PCA + chronic variable stress	5-HT neurotoxin	Wistar rats (286–360 g)	2	i.p., 21 days	0		Harro et al., 2001
PCPA	5-HT synthesis inhibitor	Long–Evans rats (260–300 g)	500–1000	For 2 days (x2, 3 days before testing)	–	Locomotion decreased	Dringenberg et al., 1995
PCPA	5-HT synthesis inhibitor	Sprague–Dawley rats (350–650 g)	100	i.p., 5 daily injections	+	(1) Weak effects; (2) Animals were tested on 5 consecutive days	Angrini et al., 1998
PCPA	5-HT synthesis inhibitor	Wistar rats (180–200 g)	50–300	i.p., twice for 2 days	0		Nazar et al., 1999b
PCPA	5-HT synthesis inhibitor	Wistar rats (180–200 g)	150	i.p., twice for 2 days	0		Nazar et al., 1999b
PCPA + Picrotoxin (0,1 μg)	5-HT synthesis inhibitor	Wistar rats (180–200 g)	150	i.p., twice for 2 days	0	No interaction	Nazar et al., 1999a,b
Pinoline	5-HT reuptake inhibitor	Wistar rats (270–350 g)	15	i.p.	–		Pähkla et al., 1996
Pizotifen	Non-selective 5-HT antagonist	Wistar rats (200–220 g)	0.63–10	s.c.	0		Meert et al., 1997
Polyclonal anti-5-HT-moduline	Decreases 5-HT release	Swiss mice (28–32 g)	5 μl	i.c.v.	+		Grimaldi et al., 1999
Propranolol	Non-selective 5-HT_{1A} antagonist	Swiss–Webster mice (6–8 weeks)	10	s.c.	–	Latency to emerge after restraint stress	Stone et al., 1995

(continued on next page)

Table 2 (*continued*)

Drug	Mechanism	Animals	Doses	Routes	Effects	Comments	Reference
Propranolol	Non-selective 5-HT_{1A} antagonist	Sprague–Dawley rats (200–250 g)	10	i.p.	+	Locomotion increased	Lucki et al., 1989
Propranolol	Non-selective 5-HT_{1A} antagonist	Sprague–Dawley rats (350–650 g)	5–20	i.p., 5 daily injections	+	(1) The D, L isomer was used; (2) animals were tested on 5 consecutive days	Angrini et al., 1998
Propranolol	Non-selective 5-HT_{1A} antagonist	Wistar rats (175–225 g)	0.3–1	i.p.	+	Latency to eat in the open field was reduced	Rex et al., 1998
Quipazine	Non-selective ligand	Rats (180–220 g)	10–20 μg	Nucleus accumbens	–		Plaznik et al., 1991
R 56413	5-HT_2 antagonist	Rats	0.01–0.63	?	+		Meert and Colpaert, 1986
Ritanserin	5-HT_2 antagonist	Wistar rats (220–240 g)	2.5–10	s.c.	–	Sedation ?	Meert, 1992
Ritanserin	5-HT_2 antagonist	Wistar rats (250–280 g)	0.01–40	s.c.	+		Meert and Colpaert, 1986
Ritanserin	5-HT_2 antagonist	Rats	0.04–10	?	+		Meert and Colpaert, 1986
Ritanserin	5-HT_2 antagonist	Wistar rats (220–240 g)	0.04–0.63	s.c.	+		Meert, 1992
Ritanserin	5-HT_2 antagonist	Wistar rats (180–220 g)	1–5	i.p.	+	65 dB noise	Stefanski et al., 1992
Ritanserin	5-HT_2 antagonist	Rats	5	?	+		Stefanski et al., 1992
Ritanserin	5-HT_2 antagonist	Wistar rats (200–220 g)	0.63–10	s.c.	0		Meert et al., 1997
Ritanserin	5-HT_2 antagonist	Wistar rats (175–225 g)	0.125–0.25	i.p.	+	Latency to eat in the open field was reduced	Rex et al., 1998
TFMPP	Non-selective agonist	Wistar rats (200–250 g)	1–5	i.p.	–	Sedation?	Klodzinska et al., 1989
TFMPP	Non-selective agonist	Sprague–Dawley rats (200–250 g)	2.5–5	i.p.	–	Locomotion decreased	Lucki et al., 1989
Tropisetron	5-HT_3 antagonist	Wistar rats (250–270 g)	0.187–20	i.p.	0		Papp and Przegalinski, 1989
Tropisetron	5-HT_3 antagonist	Wistar rats	0.000001–0.0001	Hippocampus	0		Stefanski et al., 1993
Tropisetron	5-HT_3 antagonist	Rats		Accumbens	+		Plaznik et al., 1991
Tropisetron	5-HT_3 antagonist	Wistar rats (180–220 g)	0.0001–0.01	i.p.	+	65 dB noise	Stefanski et al., 1992
Tropisetron	5-HT_3 antagonist	Rats	0.001–0.1	?	+		Stefanski et al., 1992
Tropisetron	5-HT_3 antagonist	Wistar rats	0.000001–0.00001	Nucleus accumbens septi	+		Stefanski et al., 1993
Tropisetron	5-HT_3 antagonist	Wistar rats	0.000005	Nucleus accumbens septi	+	+5,7-DHT	Stefanski et al., 1993
Tropisetron	5-HT_3 antagonist	Wistar rats (175–225 g)	0.001–0.01	i.p.	+	Latency to eat in the open field was reduced	Rex et al., 1998
WAY 100635	5-HT_{1A} antagonist	Male and female C57BL6/J ×129/sv mice	0.03–0.3		+		Ramboz et al., 1998

+, Anxiolytic-like effect; –, anxiogenic-like effect; 0, no anxiolytic or anxiogenic-like effects (in some cases, non-specific effects can be observed but this will be specified in the "comment" column); 5-HT, 5-hydroxytryptamine (serotonin); DPAG, dorsal periaqueductal gray; i.p., intraperitoneal; p.o., per os; s.c., subcutaneous; i.v., intravenous; i.c.v., intracerebroventricular. Data obtained from G. Griebel, personal database.

example, for chickens, most of the studies report no effect or anxiogenic-like effects after treatment with anxiolytic compounds.

Interestingly, triazolopyridazines such as alprazolam or adinazolam produce effects very different from those of classical benzodiazepine receptor agonists: approximately 1/3 of the studies reported anxiolytic-like effects, 1/3 no effect and 1/3 anxiogenic effects. This variability may be related to the clinical features of these compounds which are well known to be active in anxiety disorders such as for example panic attacks (Uhlenhuth et al., 1989; Westenberg, 1996), rather than on normal anxiety. Indeed, it is to be noted that normal and pathological anxiety have a very different phenomenology and are underlined by very different mechanisms. They are thus modelized in animals by very different situations (Belzung and Griebel, 2001). For example, the mouse defense test battery in mice seem to model certain aspects of panic attacks (Griebel et al., 1995, 1997, 1998), the free exploratory test situation models some aspects some aspects of generalized anxiety (Belzung and Berton, 1997) and exposure of rodents to cat may rather modelize post-traumatic stress disorder (Belzung et al., 2001). One may therefore suggest that the open field test may not be relevant to model such diseases, as it does not offer predictive validity for such disorders. The same poor ability of the open field to detect anxiolytic-like effects of benzodiazepine partial and selective agonists should be noted, which further emphasizes the failure of this procedure to fully mimic the clinical efficacy of the model.

As to benzodiazepine receptor inverse agonists, the situation mirrors that of agonists, as 62.5% of the studies reveal anxiogenic-like effects. Finally, most of the studies on the action of neurosteroid ligands (74%) failed to detect any activity of these compounds. This is one more argument in favor of the idea that the open field may not model various aspects of anxiety disorders, as neurosteroid abnormalities have been specifically detected in some anxiety disorders. For example, patients with generalized anxiety disorder have significantly lower levels of pregnenolone sulfate than do control subjects (Semeniuk et al., 2001).

Finally, 57% of the studies involving $GABA_A$ receptor agonists failed to reveal intrinsic effects of such compounds. This is not very surprising, as GABA receptor agonists are not endowed with anxiolytic activity (Ågmo et al., 1991). The fact that 43% of the studies revealed anxiolytic-like effects with such compounds is surprising and shows that this model may in some cases be sensitive to false positive effects. Barbiturates are generally anxiolytic in the open field (75% of the studies), which parallels clinical data.

3. Effects of serotonin-like acting drugs

Considerable research has been undertaken since the early 1980s on the anxiolytic-like activity of drugs acting on serotonin (5-HT) neurotransmission, particularly compounds that bind selectively on 5-HT_{1A} receptors (agonists, but also antagonists) or inhibit 5-HT reuptake (Selective Serotonin Reuptake Inhibitors) (see Griebel, 1995, 1996, 1999a; Belzung, 2001 for reviews). A summary of the studies investigating the effects of these compounds in animals tested in an open field is presented in Table 2.

Parenteral administration of full or partial agonists of 5-HT_{1A} receptors generally induces anxiolytic-like effects in animals subjected to the open field. Indeed, 8-hydroxydipropylaminotetralin (8-OH-DPAT) elicited anxiolytic-like effects in 62.5% of the studies (exactly as benzodiazepine full agonists) and partial agonists such as buspirone, gepirone or ipsapirone were anxiolytic in 73.3% of the studies. This can be compared to the effects of these compounds in other animal models of anxiety. For example, we have shown that 5-HT_{1A} receptors agonists had anxiolytic-like activity in 74% of the preclinical studies (Belzung, 2001). So, one may conclude that the ability of the open field to detect anxiolysis of 5-HT_{1A} receptors agonists is exactly the same as that of other animal models of anxiety, which renders this model suitable for the assessment of the anxiolytic-like activity of such compounds.

However, this does not extend to other putative anxiolytic treatments. Indeed, chronic administration of not only Selective Serotonin Reuptake Inhibitors (fluoxetine, amitriptyline, clomipramine, paroxetine) but also of other types of antidepressants such as the tricyclic, imipramine, never elicited anxiolytic-like effects. In 89% of the studies, no effects were obtained after such treatments while in some cases anxiogenic actions could be observed. This parallels results obtained with other animal models of anxiety-like behavior. One must remember that the open field test was pharmacologically validated with classical benzodiazepines such as chlordiazepoxide and diazepam that are effective in the treatment of generalized anxiety disorder. In the clinic, chronic Selective Serotonin Reuptake Inhibitors and tricyclics have been used successfully in the treatment of panic attacks (Westenberg, 1996; Wagstaff et al., 2002a,b), social phobia, post-traumatic stress disorder (Wagstaff et al., 2002a,b) and obsessive-compulsive disorders (Thomsen, 2000; Wagstaff et al., 2002a,b), which are anxiety disorders. This further emphasizes that the open field test may not be a model of pathological anxiety, as it has no predictive validity for such disorders.

Regarding the effects of 5-HT_2 receptor antagonists, only ritanserin induced anxiolytic-like effects (75% of the studies) while no effects were observed with other compounds such as ketanserin, methysergide, mianserin or RO 56413. This parallels the classical reports of the high variability of serotonin effects in the clinic. Finally, non-specific 5-HT receptor agonists were always anxiogenic while 5-HT_{1A} receptor antagonists elicited anxiolysis in 56% of the studies and no effect in the other cases. This may be related to differences in mechanisms (some antagonists selectively bind to 5-HT_{1A} receptors while others also have an affinity for other neurotransmitter receptors).

Table 3
Effects of CRF ligands on animals subjected to the open field test

Drug	Mechanism	Animals	Doses (mg/kg)	Routes	Effects	Comments	Reference
α-hel CRF_{9-41}	$CRF_{1/2}$ antagonist	Wistar rats (310–330 g)	5 μg/5 μl	i.c.v.	0		Kumar and Karanth, 1996
α-hel CRF_{9-41}	$CRF_{1/2}$ antagonist	BALB/c mice (10 weeks)	0.8–8 nmol	i.c.v.	0		Moreau et al., 1997
Antisense ODN	CRF gene inhibition	Sprague–Dawley rats (200–250 g)	1 nmol	hippocampus, 4 injections	+	Increased exploration	Wu et al., 1997
CRF	Endogenous peptide	Wistar rats (200–230 g)	0.15 nmol/2 μl	i.c.v.	–		Sutton et al., 1982
CRF	Endogenous peptide	Sprague–Dawley rats (300 g)	150 pmol/2 μl	i.c.v.	–		Britton et al., 1982
CRF	Endogenous peptide	Sprague–Dawley rats (180–230 g)	0.01–1 μg/1 μl	amygdala	–	Decrease in locomotor activity, rearing and hole poking	Liang and Lee, 1988
CRF	Endogenous peptide	BALB/c mice (20–25 g)	0.01 μg/0.4 μl	dendate gyrus of hippocampus	–	Increased locomotor activity in the center	Lee and Tsai, 1989
CRF	Endogenous peptide	BALB/c mice (20–25 g)	0.02 μg/0.5 μl	amygdala	–	Increased locomotor activity in the center	Lee and Tsai, 1989
CRF	Endogenous peptide	Sprague–Dawley rats (250 g)	60 pmol/2 μl	i.c.v.	–		Britton and Indyk, 1990
CRF	Endogenous peptide	Wistar rats (310–330 g)	0.1–0.4 μg/5 μl	i.c.v.	–		Kumar and Karanth, 1996
CRF	Endogenous peptide	BALB/c mice (20–25 g)	0.2 μg/2 μl	i.c.v.	–	Increased center region activity	Lee et al., 1987
CRF	Endogenous peptide	Wistar rats (200–230 g)	0.015–7.5 nmol/2 μl	s.c.	0		Sutton et al., 1982
CRF	Endogenous peptide	BALB/c mice (20–25 g)	0.05 μg/0.7 μl	caudate nucleus	0		Lee and Tsai, 1989
CRF + α-hel CRF_{9-41} (5 μg/5 μl)	Endogenous peptide	Wistar rats (310–330 g)	0.1–0.4 μg	i.c.v.	(+)		Kumar and Karanth, 1996
CRF + Diazepam (2 mg/kg)	Endogenous peptide	BALB/c mice (20–25 g)	0.2 μg/2 μl	i.c.v.	(+)		Lee et al., 1987
Urocortin	Endogenous CRF_2 ligand	BALB/c mice (10 weeks)	0.06 nmol	i.c.v.	–		Moreau et al., 1997
Urocortin + α-hel CRF_{9-41} (2.6–8 nmol)	Endogenous CRF_2 ligand	BALB/c mice (10 weeks)	0.06 nmol	i.c.v.	(+)		Moreau et al., 1997
Urocortin + Diazepam (0.1–1)	Endogenous CRF_2 ligand	BALB/c mice (10 weeks)	0.06 nmol	i.c.v.	(+)		Moreau et al., 1997
Antisense ODN + CRF (0.5 μg)	Blockade of CRF_1 receptor translation	Wistar rats (200–250 g)	0.5 μl/h	minipumps, 3 days	(+)		Skutella et al., 1998
CRF	Endogenous peptide	Wistar rats (200–250 g)	0.5 μg	i.c.v.	–		Skutella et al., 1998
Urocortin + CRF-OH	Endogenous CRF_2 ligand	Rats	0.1 μg	i.c.v.	0		Zorrilla et al., 1998
Urocortin + CRF_{6-33}	Endogenous CRF_2 ligand	Rats	0.1 μg	i.c.v.	0		Zorrilla et al., 1998

+, Anxiolitic-like effect; –, anxiogenic-like effect; 0, no anxiolytic or anxiogenic-like effects (in some cases, non-specific effects can be observed but this will be specified in the "comment" column); (+) antagonism of anxiogenic-like effects; (–), antagonism of anxiolytic-like effects; s.c., subcutaneous; i.c.v., intracerebroventricular. Data obtained from G. Griebel, personal database.

Finally, in situ administration of 5-HT_{1A} receptor agonists in limbic structures such as the hippocampus was always anxiolytic. This parallels the effects observed after stimulation of the 5-HT_{1A} pre-synaptic receptors in other rodent models of anxiety (see Griebel, 1995 for a review) and suggests that the anxiolytic activity of 5-HT_{1A} receptors may be related to a pre-synaptic target.

4. Effects of neuropeptide receptor ligands

Recently, the rapid advances in neuropeptide research have stimulated interest in the ability of some neuropeptides to act as anxiolytics (see Griebel, 1999b for an excellent review). Interest has focused on CRF receptor ligands, on cholecystokinin, neuropeptide Y, tachykinin (especially neurokinin) as well as on glucocorticoid and mineralocorticoid receptor ligands.

Studies investigating the effects of CRF receptor ligands are presented in Table 3. This table shows clearly that all the studies involving i.c.v. injections of CRF found anxiogenic effects of the neuropeptide. The sole study that found no intrinsic activity had assessed the effects of s.c. injected CRF so that the failure of CRF to induce anxiogenesis may be attributed to rapid degradation of the peptide. All these anxiogenic effects may be due to the interaction of CRF with molecular targets situated in the limbic structures as anxiogenic effects were obtained after intra-amygdala and intra-hippocampal injections of the peptide. Unfortunately, no study investigated the effects of specific CRF receptor antagonists, so that it is very difficult to conclude further about the ability of the open field test to detect anxiolytic activity of such ligands.

Data for the effects of other neuropeptide receptor ligands are in Table 4. We found only 15 studies describing such effects, 9 of which concerned the effects of neuro-

Table 4
Effects of non-CRF neuropeptide ligand on animals subjected to the open field test

Drug	Mechanism	Animals	Doses	Routes	Effects	Comments	Reference
ANP	Neuropeptide	Wistar rats (180–200 g)	200–500 ng/5 μl	i.c.v.	+		Bhattacharya et al., 1996
Atriopeptin II	Residue peptide	Wistar rats (220–260 g)	5–10 μg/rat	i.c.v.	+		Poggioli et al., 1992
BIBP3226	Y_1 antagonist	Wistar rats (280–350 g)	0.5 μg	DPAG	0		Kask et al., 1998
BIBP3226	Y_1 antagonist	Wistar rats (280–350 g)		i.c.v.	0		Kask et al., 1998
BIBP3226	Y_1 antagonist	Wistar rats (300–450 g)	5 μg/6.5 μl	i.c.v.	0		Kask et al., 1998
BIBP3226	Y_1 antagonist	Wistar rats (300–450 g)	0.5 μg/6.5 μl	DPAG	0		Kask et al., 1998
CCK-8s	CCK1/B agonist	Sprague–Dawley rats (200–220 g)	100 pmol/1 μl	median nucleus accumbens	–		Daugé et al., 1989
CCK-8s	CCK1/B agonist	Sprague–Dawley rats (200–220 g)	1 fmol–100 pmol/1 μl	median nucleus accumbens	0	Rats were habituated to the environment	Daugé et al., 1989
CGP71683A	Y_5 antagonist	Wistar rats (280–350 g)	10	i.p.	–	Rats exposed to the elevated plus maze before open field testing	Kask et al., 2001
GR 64349	NK_2 agonist	Rats	100–1000 pmol	dorsal raphé	–		Stratton et al., 1993
Neuropeptide Y	Endogenous peptide	Sprague–Dawley rats (220–250 g)	1–4 nmol/5 μl	i.c.v.	?	NPY decreased spontaneous activity	Heilig and Murison, 1987
RU28318	Mineralocorticoid antagonist	Long–Evans rats (300–400 g)	0.5 ng/0.5 μl	hippocampus	+		Bitran et al., 1998
RU28318 + Dexamethasone	Mineralocorticoid antagonist	Long–Evans rats (300–400 g)	0.5 ng/0.5 μl	hippocampus	(0)		Bitran et al., 1998
RU38486	Glucocorticoid antagonist	Long–Evans rats (300–400 g)	0.2–0.5 ng/ 0.5 μl	hippocampus	0		Bitran et al., 1998
RU38486 + Dexamethasone	Glucocorticoid antagonist	Long–Evans rats (300–400 g)	0.2–0.5 ng/ 0.5 μl	hippocampus	0		Bitran et al., 1998

+, Anxiolytic-like effect; –, anxiogenic-like effect; 0, no anxiolytic or anxiogenic-like effects (in some cases, non-specific effects could be observed but this will be specified in the "comment" column); (0) no antagonism; i.p., intraperitoneal; i.c.v., intracerebroventricular; DPAG, dorsal periaqueductal gray. Data obtained from G. Griebel, personal database.

peptide injected directly into some specific brain areas. Most of the studies concerned the effects of neuropeptide Y ligands, either neuropeptide Y Y1 receptor antagonists (BIBP3226) or neuropeptide Y Y5 receptor antagonist (CGP71683A). The neuropeptide Y Y1 receptor antagonist, administered parenterally or within the dorsal periaqueductal gray, never elicited any intrinsic action while the neuropeptide Y Y5 receptor antagonist was anxiogenic. The glucorticoid receptor antagonist did not elicit any effect when injected within the hippocampus. In fact, due to the scarcity of data, it is very difficult to reach a relevant way conclusion.

We applied the Griebel (1999b) synthesis to the preclinical studies investigating the effects of neuropeptide ligands in animal models of anxiety to calculate the proportion of articles using the open field. Surprisingly, very few used this paradigm: only 2/359 studies investigating the effects of CCK ligands, 17/343 articles investigating the effects of CRF receptors ligands; 1/51 interested in the action of NPY ligands and 1/52 in the articles studying the effects of neurokinin receptor ligands. The other studies were done with other animal models of anxiety, such as the elevated plus maze, the light–dark boxes, the mouse defense test battery or more classical conditioned conflict tests. Why? Two hypotheses can be suggested: either the open field test is no longer up-to-date (because of the availability of other tests), or was used and negative results were obtained that were not found relevant for publication. As to the first hypothesis, one may argue that this is not very probable. Indeed, in a recent review on the genetics of anxiety-like behavior in rodent models (Clement et al., 2002), we showed that the open field test was used in 30/68 studies. These studies were mostly very recent. Therefore, one may propose that neuropeptides may not have very marked anxiolytic-like effects in the open field.

5. Conclusion

Is the open field test suitable for screening anxiolytic activity of pharmacological treatments? To be a relevant model of human behavior, an animal test should fit three criteria: predictive, face and construct validity. Our review of the literature shows clearly that the open field cannot claim predictive validity for anxiety in general, as it is not sensitive to compounds (alprazolam and chronic Selective Serotonin Reuptake Inhibitors) effective in anxiety disorders such as panic, obsessional compulsive disorder, social phobias and post-traumatic stress disorder. In fact, it seems to be sensitive only to the anxiolytic effects produced by classical benzodiazepines and 5-HT_{1A} receptor agonists. Therefore, one may suggest that the open field may either be a model of the normal anxiety everyone is faced by when confronted with a stressful or threatening situation but not with the features of pathological anxiety or, alternatively, it may be a model to test the behavioral effects of classical benzodiazepines and 5-HT_{1A} agonists. However, a radical-seeming cautionary comment is needed here. Indeed, the disorders termed ‘‘Anxiety disorders’’ in the DSM-IV (1994) are called ‘‘Somatoform, stress-related and neurotic disorders’’ in the ICD-10 (1994) classification of the World Health Organization. In fact, it is possible that we are trapped by the terminology and that the psychiatric diseases termed ‘‘anxiety disorders’’ may have no relationship with anxiety-like behavior. In this case, of course, the open field may gain in predictive validity.

As to the face and construct validity of this model, one may propose that they are fulfilled. In fact, face validity implies that the anxiety response (the phenomenological aspect) observed in the animal is identical to the one observed in humans. In the open field, the observed behavior is avoidance of threatening places, which can also be observed in humans. In rodents, forced confrontation with novelty is stressful (Misslin and Cigrang, 1986). Stress induces anxiety-like behaviors, as it does in humans. So, the model may also fit construct validity (similar etiology).

In conclusion, the open field test may be a rodent model of normal anxiety, sensitive to the anxiolytic-like effects of classical benzodiazepines and 5-HT_{1A} receptor agonists but not to the effects of compounds displaying anxiolytic-like effects in the clinical entity termed ‘‘anxiety disorders’’.

Acknowledgements

The authors are thankful to Dr. G. Griebel for providing data from his personal database (Tables 2, 3 and 4).

References

Adams, P.M., 1982. Effects of perinatal chlordiazepoxide exposure on rat preweaning and postweaning behavior. Neurobehav. Toxicol. Teratol. 4, 279–282.

Ågmo, A., Pruneda, R., Guzman, M., Gutierrez, M., 1991. GABAergic drugs and conflict behavior in the rat: lack of similarities with the actions of benzodiazepines. Naunyn-Schmiedeberg’s Arch. Pharmacol. 344, 314–322.

Ahlenius, S., Larsson, K., Wijkstrom, A., 1991. Behavioral and biochemical effects of the 5-HT_{1A} receptor agonists flesinoxan and 8-OH-DPAT in the rat. Eur. J. Pharmacol. 200, 259–266.

Alleva, E., Laviola, G., Tirelli, E., Bignami, G., 1985. Short-, medium-, and long-term effects of prenatal oxazepam on neurobehavioural development of mice. Psychopharmacology 87, 434–441.

Andersen, I., Faerevik, G., Boe, K.E., Janczak, A.M., Bakken, M., 2000. Effects of diazepam on the behavior of weaned pigs in three putative models of anxiety. Appl. Anim. Behav. Sci. 68, 121–130.

Angrini, M., Leslie, J.C., Shephard, R.A., 1998. Effects of propranolol, buspirone, pCPA, reserpine, and chlordiazepoxide on open-field behavior. Pharmacol. Biochem. Behav. 59, 387–397.

Barros, H.M., Tannhauser, S.L., Tannhauser, M.A., Tannhauser, M., 1994. The effects of GABAergic drugs on grooming behaviour in the open field. Pharmacol. Toxicol. 74, 339–344.

Bast, T., Zhang, W.N., Feldon, J., 2001a. Hyperactivity, decreased startle reactivity, and disrupted prepulse inhibition following disinhibition of

the rat ventral hippocampus by the GABA(A) receptor antagonist picrotoxin. Psychopharmacology (Berl.) 156, 225–233.

Bast, T., Zhang, W.N., Feldon, J., 2001b. The ventral hippocampus and fear conditioning in rats. Different anterograde amnesias of fear after tetrodotoxin inactivation and infusion of the GABA(A) agonist muscimol. Exp. Brain Res. 139, 39–52.

Beaufour, C.C., Le Bihan, C., Hamon, M., Thiebot, M., 2001. Extracellular dopamine in the rat prefrontal cortex during reward-, punishment- and novelty-associated behaviour. Effects of diazepam. Pharmacol. Biochem. Behav. 69, 133–412.

Beckett, S.R., Lawrence, A.J., Marsden, C.A., Marshall, P.W., 1992. Attenuation of chemically induced defence response by 5-HT1 receptor agonists administered into the periaqueductal gray. Psychopharmacology (Berl.) 108, 104–110.

Belzung, C., 1999. Measuring exploratory behavior. In: Crusio, W.E., Gerlai, R.T. (Eds.), Handbook of Molecular Genetic Techniques for Brain and Behavior Research (Techniques in the Behavioral and Neural Sciences). Elsevier, Amsterdam, pp. 739–749.

Belzung, C., 2001. Rodent models of anxiety-like behaviors: are they predictive for compounds acting via non-benzodiazepine mechanisms? Curr. Opin. Investig. Drugs 2, 1108–1111.

Belzung, C., Berton, F., 1997. Further pharmacological validation of the Balb/c neophobia in the free exploratory paradigm as an animal model of trait anxiety. Behav. Pharmacol. 8, 541–548.

Belzung, C., Griebel, G., 2001. Measuring normal and pathological anxiety-like behaviour in mice: a review. Behav. Brain Res. 125, 141–149.

Belzung, C., El Hage, W., Moindrot, N., Griebel, G., 2001. Behavioral and neurochemical changes following predatory stress in mice. Neuropharmacology 41, 400–408.

Belzung, C., Griebel, G., Dubois-Carmagnat, F., Darves-Bornoz, J.M., 2002. Amino acid transmitter systems. In: D'Haenen, H., den Boer, J.A., Willner, P. (Eds.), Biological Psychiatry. Wiley, Chichester, England, pp. 915–927.

Bert, B., Fink, H., Sohr, R., Rex, A., 2001. Different effects of diazepam in Fischer rats and two stocks of Wistar rats in tests of anxiety. Pharmacol. Biochem. Behav. 70, 411–420.

Bhattacharya, S.K., Clow, A., Przyborowska, A., Halket, J., Glover, V., Sandler, M., 1991. Effect of aromatic amino acids, pentylenetetrazole and yohimbine on isatin and tribulin activity in rat brain. Neurosci. Lett. 132, 44–46.

Bhattacharya, S.K., Sen, A.P., Upadhyay, S.N., Jaiswal, A.K., 1993. Anxiolytic activity of piracetam, a nootropic agent, following subchronic administration in rodents. Indian J. Exp. Biol. 31, 902–907.

Bhattacharya, S.K., Chakrabarti, A., Sandler, M., Glover, V., 1996. Anxiolytic activity of intraventricularly administered atrial natriuretic peptide in the rat. Neuropsychopharmacology 15, 199–206.

Bhattacharya, S.K., Bhattacharya, A., Ghosal, S., 1998. Anxiogenic activity of methylenedioxymethamphetamine (Ecstasy): an experimental study. Biog. Amine. 14, 217–237.

Bitran, D., Shiekh, M., Dowd, J.A., Dugan, M.M., Renda, P., 1998. Corticosterone is permissive to the anxiolytic effect that results from the blockade of hippocampal mineralocorticoid receptors. Pharmacol. Biochem. Behav. 60, 879–887.

Boerngen-Lacerda, R., Souza-Formigoni, M.L., 2000. Does the increase in locomotion induced by ethanol indicate its stimulant or anxiolytic properties? Pharmacol. Biochem. Behav. 67, 225–232.

Borsini, F., Giuliani, S., Meli, A., 1988. Functional responses to baclofen and 4,5,6,7-tetrahydroisoxazolo (5,4-*c*) pyridin-3-ol (THIP) in rats repeatedly treated with desipramine. Pharmacol. Biochem. Behav. 29, 189–191.

Britton, D.R., Britton, K.T., 1981. A sensitive open field measure of anxiolytic drug activity. Pharmacol. Biochem. Behav. 15, 577–582.

Britton, D.R., Indyk, E., 1990. Central effects of corticotropin releasing factor (CRF): evidence for similar interactions with environmental novelty and with caffeine. Psychopharmacology (Berl.) 101, 366–370.

Britton, D.R., Koob, G.F., Rivier, J., Vale, W., 1982. Intraventricular corticotropin-releasing factor enhances behavioral effects of novelty. Life Sci. 31, 363–367.

Broderick, P.A., Hope, O., Jeannot, P., 1998. Mechanism of triazolobenzodiazepine and benzodiazepine action in anxiety and depression: behavioral studies with concomitant in vivo CA1 hippocampal norepinephrine and serotonin release detection in the behaving animal. Prog. Neuropsychopharmacol. Biol. Psychiatry 22, 353–386.

Bruhwyler, J., 1990. Anxiolytic potential of a microgram dose of chlordiazepoxide in the open-field test. Eur. J. Pharmacol. 187, 547–549.

Bruhwyler, J., Chleide, E., Houbeau, G., Mercier, M., 1991. Stimulant effect of the beta-carboline FG 7142 in the open-field test. Eur. J. Pharmacol. 200, 183–185.

Bruijnzeel, A.W., Stam, R., Wiegant, V.M., 2001. Effect of a benzodiazepine receptor agonist and corticotropin-releasing hormone receptor antagonists on long-term foot-shock-induced increase in defensive withdrawal behavior. Psychopharmacology (Berl.) 158, 132–139.

Cannizzaro, C., Martire, M., Cannizzaro, E., Provenzano, G., Gagliano, M., Carollo, A., Mineo, A., Steardo, L., 2001. Long-lasting handling affects behavioural reactivity in adult rats of both sexes prenatally exposed to diazepam. Brain Res. 904, 225–233.

Car, H., Kuziemka, L., Eska, M., Wisniewski, K., 1996. The NMDA and GABA-A receptors in behavioral activity of rats. Acta Physiol. Hung. 84, 269–270.

Carli, M., Prontera, C., Samanin, R., 1989. Effect of 5-HT1A agonists on stress-induced deficit in open field locomotor activity of rats: evidence that this model identifies anxiolytic-like activity. Neuropharmacology 28, 471–476.

Carli, M., Tatarczynska, E., Cervo, L., Samanin, R., 1993. Stimulation of hippocampal 5-HT1A receptors causes amnesia and anxiolytic-like but not antidepressant-like effects in the rat. Eur. J. Pharmacol. 234, 215–221.

Chesley, S., Lumpkin, M., Schatzki, A., Galpern, W.R., Greenblatt, D.J., Shader, R.I., Miller, L.G., 1991. Prenatal exposure to benzodiazepine: I. Prenatal exposure to lorazepam in mice alters open-field activity and GABAA receptor function. Neuropharmacology 30, 53–58.

Choleris, E., Thomas, A.W., Kavaliers, M., Prato, F.S., 2001. A detailed ethological analysis of the mouse open field test: effects of diazepam, chlordiazepoxide and an extremely low frequency pulsed magnetic field. Neurosci. Biobehav. Rev. 25, 235–260.

Clement, Y., Calatayud, F., Belzung, C., 2002. Genetic basis of anxiety-like behaviour: a critical review. Brain Res. Bull. 57, 57–71.

Coscina, D.V., Nobrega, J.N., 1989. Effects of lateral hypothalamic lesions on the anorexia induced by ethanolamine-*O*-sulfate. Pharmacol. Biochem. Behav. 32, 275–281.

Crawley, J.N., 1981. Neuropharmacologic specificity of a simple animal model for the behavioral actions of benzodiazepines. Pharmacol. Biochem. Behav. 15, 695–699.

Czlonkowska, A.I., Sienkiewicz-Jarosz, H., Siemiatkowski, M., Bidzinski, A., 1999. The effects of neurosteroids on rat behavior and 3H-muscimol binding in the brain. Pharmacol. Biochem. Behav. 63, 639–646.

Daugé, V., Dor, A., Feger, J., Roques, B.P., 1989. The behavioral effects of CCK8 injected into the medial nucleus accumbens are dependent on the motivational state of the rat. Eur. J. Pharmacol. 163, 25–32.

De Angelis, L., 1996. Experimental anxiety and antidepressant drugs: the effects of moclobemide, a selective reversible MAO-A inhibitor, fluoxetine and imipramine in mice. Naunyn-Schmiedeberg's Arch. Pharmacol. 354, 379–383.

De Angelis, L., Bertolissi, M., Nardini, G., Traversa, U., Vertua, R., 1982. Interaction of caffeine with benzodiazepines: behavioral effects in mice. Arch. Int. Pharmacodyn. Ther. 255, 89–102.

Delini-Stula, A., Hunn, C., 1988. Differential effects of anxiolytics and beta-receptor blocking drugs on novelty-oriented ("neophobic") behavior in the rat. Pharmacopsychiatry 21, 186–191.

Depaulis, A., Vergnes, M., 1986. Elicitation of intraspecific defensive behaviors in the rat by microinjection of picrotoxin, a gamma-aminobutyric acid antagonist, into the midbrain periaqueductal gray matter. Brain Res. 367, 87–95.

De Souza Spinosa, H., Gerenutti, M., Bernardi, M.M., 2000. Anxiolytic and anticonvulsant properties of doramectin in rats: behavioral and neurochemistric evaluations. Comp. Biochem. Physiol., Toxicol. Pharmacol. 127, 359–366.

Dringenberg, H.C., Hargreaves, E.L., Baker, G.B., Cooley, R.K., Vanderwolf, C.H., 1995. *p*-Chlorophenylalanine-induced serotonin depletion: reduction in exploratory locomotion but no obvious sensory-motor deficits. Behav. Brain Res. 68, 229–237.

DSM-IV, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Pyschiatric Association, Washington, DC.

Durand, M., Berton, O., Aguerre, S., Edno, L., Combourieu, I., Mormede, P., Chaouloff, F., 1999. Effects of repeated fluoxetine on anxiety-related behaviours, central serotonergic systems, and the corticotropic axis in SHR and WKY rats. Neuropharmacology 38, 893–907.

Durand, M., Aguerre, S., Fernandez, F., Edno, L., Combourieu, I., Mormede, P., Chaouloff, F., 2000. Strain-dependent neurochemical and neuroendocrine effects of desipramine, but not fluoxetine or imipramine, in spontaneously hypertensive and Wistar–Kyoto rats. Neuropharmacology 39, 2464–2477.

Dwyer, K.D., Roy, E.J., 1993. Juvenile desipramine reduces adult sensitivity to imipramine in two behavioral tests. Pharmacol. Biochem. Behav. 45, 201–217.

Fahey, J.M., Pritchard, G.A., Grassi, J.M., Pratt, J.S., Shader, R.I., Greenblatt, D.J., 2001. Pharmacodynamic and receptor binding changes during chronic lorazepam administration. Pharmacol. Biochem. Behav. 69, 1–8.

Fahey, J.M., Pritchard, G.A., Pratt, J.S., Shader, R.I., Greenblatt, D.J., 1999. Lorazepam attenuates the behavioral effects of dizocilpine. Pharmacol. Biochem. Behav. 62, 103–110.

Fernandez-Teruel, A., Escorihuela, R.M., Boix, F., Tobena, A., 1990. Picrotoxin changes the effects of imipramine and desipramine in rats in the forced swimming test. Eur. J. Pharmacol. 181, 35–41.

Ferre, P., Escorihuela, R.M., Tobena, A., Fernandez-Teruel, A., 1996. Evaluation of perinatal flumazenil effects on the behavior of female RLA/Verh rats in anxiety tests and shuttle box avoidance. Pharmacol. Biochem. Behav. 55, 475–480.

File, S.E., Tucker, J.C., 1983. Lorazepam treatment in the neonatal rat alters submissive behavior in adulthood. Neurobehav. Toxicol. Teratol. 5, 289–294.

Fiore, M., Dell'Omo, G., Alleva, E., Lipp, H.P., 1995. A comparison of behavioural effects of prenatally administered oxazepam in mice exposed to open-fields in the laboratory and the real world. Psychopharmacology (Berl.) 122, 72–77.

Fonseca, N.M., Sell, A.B., Carlini, E.A., 1976. Differential behavioral responses of male and female adult rats treated with five psychotropic drugs in the neonatal stage. Psychopharmacologia 46, 263–268.

Frye, C.A., Lacey, E.H., 1999. The neurosteroids DHEA and DHEAS may influence cognitive performance by altering affective state. Physiol. Behav. 66, 85–92.

Frye, C.A., Sturgis, J.D., 1995. Neurosteroids affect spatial/reference, working, and long-term memory of female rats. Neurobiol. Learn. Mem. 64, 83–96.

Gai, N., Grimm, V.E., 1982. The effect of prenatal exposure to diazepam on aspects of postnatal development and behavior in rats. Psychopharmacology 78, 225–229.

Galpern, W.R., Lumpkin, M., Greenblatt, D.J., Shader, R.I., Miller, L.G., 1991. Chronic benzodiazepine administration: VII. Behavioral tolerance and withdrawal and receptor alterations associated with clonazepam administration. Psychopharmacology 104, 225–230.

Garcia-Gil, L., De Miguel, R., Romero, J., Perez, A., Ramos, J.A., Fernandez-Ruiz, J.J., 1999. Perinatal delta9-tetrahydrocannabinol exposure augmented the magnitude of motor inhibition caused by GABA(B), but not GABA(A), receptor agonists in adult rats. Neurotoxicol. Teratol. 21, 277–283.

Gentsch, C., Lichteiner, M., Feer, H., 1989. Behavioral effects of yohimbine and chlordiazepoxide: dependence on the rat's previous familiarization with the test conditions. Neuropsychobiology 22, 101–107.

Griebel, G., 1995. 5-Hydroxytryptamine-interacting drugs in animal models of anxiety disorders: more than 30 years of research. Pharmacol. Ther. 65, 319–395.

Griebel, G., 1996. Variability in the effects of 5-HT-related compounds in experimental models of anxiety: evidence for multiple mechanisms of 5-HT in anxiety or never ending story? Pol. J. Pharmacol. 48, 129–136.

Griebel, G., 1999a. 5-HT_{1A} receptor blockers as potential drug candidates for the treatment of anxiety disorders. Drug News Perspect. 12, 484–490.

Griebel, G., 1999b. Is there a future for neuropeptide receptor ligands in the treatment of anxiety disorders? Pharmacol. Ther. 82, 1–61.

Griebel, G., Blanchard, D.C., Jung, A., Lee, J.C., Masuda, C.K., Blanchard, R.J., 1995. Further evidence that the mouse defense test battery is useful for screening anxiolytic and panicolytic drugs: effects of acute and chronic treatment with alprazolam. Neuropharmacology 34, 1625–1633.

Griebel, G., Perrault, G., Sanger, D.J., 1997. Behavioural profiles of the reversible monoamine-oxidase-A inhibitors befloxatone and moclobemide in an experimental model for screening anxiolytic and anti-panic drugs. Psychopharmacology 131, 180–186.

Griebel, G., Curet, O., Perrault, G., Sanger, D.J., 1998. Behavioral effects of phenelzine in an experimental model for screening anxiolytic and anti-panic drugs: correlation with changes in monoamine-oxidase activity and monoamine levels. Neuropharmacology 37, 927–935.

Grimaldi, B., Bonnin, A., Fillion, M.P., Prudhomme, N., Fillion, G., 1999. 5-Hydroxytryptamine-moduline: a novel endogenous peptide involved in the control of anxiety. Neuroscience 93, 1223–1225.

Guillamon, A., Cales, J.M., Rodriguez-Zafra, M., Perez-Laso, C., Caminero, A., Izquierdo, M.A., Segovia, S., 1990. Effects of perinatal diazepam administration on two sexually dimorphic nonreproductive behaviors. Brain Res. Bull. 25, 913–916.

Hall, C.S., 1934. Emotional behavior in the rat: I. Defecation and urination as measures of individual differences in emotionality. J. Comp. Psychol. 18, 385–403.

Handa, R.J., George, M., Gordon, B.H., Campbell, D.B., Lorens, S.A., 1996. Responses to novelty stress in female F344 rats: effects of age and D-fenfluramine treatment. Pharmacol. Biochem. Behav. 53, 641–664.

Hard, E., Engel, J., Larsson, K., Musi, B., 1985. Effect of diazepam, apomorphine and haloperidol on the audiogenic immobility reaction and on the open field behavior. Psychopharmacology 85, 106–110.

Harro, J., Tonissaar, M., Eller, M., Kask, A., Oreland, L., 2001. Chronic variable stress and partial 5-HT denervation by parachloroamphetamine treatment in the rat: effects on behavior and monoamine neurochemistry. Brain Res. 899, 227–239.

Heilig, M., Murison, R., 1987. Intracerebroventricular neuropeptide Y suppresses open field and home cage activity in the rat. Regul. Pept. 19, 221–231.

Hiltunen, A.J., Jarbe, T.U., 1986. Discrimination of Ro 11-6896, chlordiazepoxide and ethanol in gerbils: generalization and antagonism tests. Psychopharmacology 89, 284–290.

Horvath, K., Andrasi, F., Botka, P., Hamori, T., 1992. Anxiolytic profile of girisopam and GYKI 52,322 (EGIS 6775). Comparison with chlordiazepoxide and buspirone. Acta Physiol. Hung. 79, 153–161.

Hughes, R.N., 1993. Effects on open-field behavior of diazepam and buspirone alone and in combination with chronic caffeine. Life Sci. 53, 1217–1225.

Huttunen, P., Myers, R.D., 1986. Tetrahydro-beta-carboline micro-injected into the hippocampus induces an anxiety-like state in the rat. Pharmacol. Biochem. Behav. 24, 1733–1738.

ICD-10, 1994. International Statistical Classification of Diseases and Related Health Problems (10th Revision). WHO Publications.

Jähkel, M., Oehler, J., Schumacher, H.E., 1994. Influence of nootropic and antidepressive drugs on open field and running wheel behavior in spontaneously high and low active mice. Pharmacol. Biochem. Behav. 49, 263–269.

Jarbe, T.U., Johansson, J.O., 1977. Pentobarbital, diazepam and bemegride:

their effects on open-field behavior in the gerbil (Meriones unguiculatus). Arch. Int. Pharmacodyn. Ther. 225, 88–97.
June, H.L., Lewis, M.J., 1989. Ro15-4513 enhances and attenuates motor stimulant effects of ethanol in rats. Alcohol 6, 245–248.
June, H.L., Johnson, L.T., Lewis, M.J., 1989. Ro15-4513 antagonizes depression of open-field horizontal activity by ethanol in rats. Alcohol 6, 335–337.
June, H.L., Cason, C.R., Cheatham, G., Lui, R., Gan, T., Cook, J.M., 1998. GABAA-benzodiazepine receptors in the striatum are involved in the sedation produced by a moderate, but not an intoxicating ethanol dose in outbred Wistar rats. Brain Res. 794, 103–118.
Kask, A., Rago, L., Harro, J., 1998. Anxiogenic-like effect of the NPY Y1 receptor antagonist BIBP3226 administered into the dorsal periaqueductal gray matter in rats. Regul. Pept. 75–76, 255–262.
Kask, A., Vasar, E., Heidmets, L.T., Allikmets, L., Wikberg, J.E., 2001. Neuropeptide Y Y(5) receptor antagonist CGP71683A: the effects on food intake and anxiety-related behavior in the rat. Eur. J. Pharmacol. 414, 215–224.
Kemble, E.D., Gibson, B.M., Rawleigh, J.M., 1991. Effects of eltoprazine hydrochloride on exploratory behavior and social attraction in mice. Pharmacol. Biochem. Behav. 38, 759–762.
Khisti, R.T., Chopde, C.T., Jain, S.P., 2000. Antidepressant-like effect of the neurosteroid 3alpha-hydroxy-5alpha-pregnan-20-one in mice forced swim test. Pharmacol. Biochem. Behav. 67, 137–143.
Klodzinska, A., Jaros, T., Chojnacka-Wojcik, E., Maj, J., 1989. Exploratory hypoactivity induced by *m*-trifluoromethylphenylpiperazine (TFMPP) and *m*-chlorophenylpiperazine (*m*-CPP). J. Neural Transm., Parkinson's Dis. Dement. Sect. 1, 207–218.
Knapp, D.J., Benjamin, D., Pohorecky, L.A., 1992. Effects of gepirone on ethanol consumption, exploratory behavior, and motor performance in rats. Drug Dev. Res. 26, 319–341.
Kopp, C., Misslin, R., Vogel, E., Rettori, M.C., Delagrange, P., Guardiola-Lemaître, B., 1997. Effects of day-length variations on emotional responses toward unfamiliarity in Swiss mice. Behav. Proc. 41, 151–157.
Kumar, K.B., Karanth, K.S., 1996. Alpha-helical CRF blocks differential influence of corticotropin releasing factor (CRF) on appetitive and aversive memory retrieval in rats. J. Neural Transm. 103, 1117–1126.
Lambadjieva, N.D., 1998. Influence of testosterone on some behavioral reactions of male immature rats. Methods Find. Exp. Clin. Pharmacol. 20, 673–677.
Lambadjieva, N.D., 1999. Influence of testosterone on some behavioral reactions of male immature rats exposed to continual light. Methods Find. Exp. Clin. Pharmacol. 21, 17–20.
Laviola, G., Pick, C.G., Yanai, J., Alleva, E., 1992. Eight-arm maze performance, neophobia, and hippocampal cholinergic alterations after prenatal oxazepam in mice. Brain Res. Bull. 29, 609–616.
Lee, E.H., Tsai, M.J., 1989. The hippocampus and amygdala mediate the locomotor stimulating effects of corticotropin-releasing factor in mice. Behav. Neural Biol. 51, 412–423.
Lee, E.H., Tang, Y.P., Chai, C.Y., 1987. Stress and corticotropin-releasing factor potentiate center region activity of mice in an open field. Psychopharmacology (Berl.) 93, 320–323.
Liang, K.C., Lee, E.H., 1988. Intra-amygdala injections of corticotropin releasing factor facilitate inhibitory avoidance learning and reduce exploratory behavior in rats. Psychopharmacology (Berl.) 96, 232–236.
Lopez, F., Miller, L.G., Greenblatt, D.J., Paul, S.M., Shader, R.I., 1988. Low-dose alprazolam augments motor activity in mice. Pharmacol. Biochem. Behav. 30, 511–513.
Lopez, F., Miller, L.G., Greenblatt, D.J., Schatzki, A., Lumpkin, M., Shader, R.I., 1992. Chronic low-dose alprazolam augments gamma-aminobutyric acid(A) receptor function. J. Clin. Psychopharmacol. 12, 119–123.
Lucki, I., Ward, H.R., Frazer, A., 1989. Effect of 1-(*m*-chlorophenyl)piperazine and 1-(*m*-trifluoromethylphenyl)piperazine on locomotor activity. J. Pharmacol. Exp. Ther. 249, 155–164.
Mar, A., Spreekmeester, E., Rochford, J., 2000. Antidepressants preferentially enhance habituation to novelty in the olfactory bulbectomized rat. Psychopharmacologia 150, 52–60.
Marin, R.H., Martijena, I.D., Arce, A., 1997. Effect of diazepam and A beta-carboline on open-field and T-maze behaviors in 2-day-old chicks. Pharmacol. Biochem. Behav. 58, 915–921.
Matsubara, K., Matsushita, A., 1982. Changes in ambulatory activities and muscle relaxation in rats after repeated doses of diazepam. Psychopharmacology 77, 279–283.
Matto, V., Allikmets, L., 1999. Acute and chronic citalopram treatment differently modulates rat exploratory behavior in the exploration box test: no evidence for increased anxiety or changes in the [3H]raclopride binding. Pharmacology 58, 59–69.
McCarthy, M.M., Felzenberg, E., Robbins, A., Pfaff, D.W., Schwartz-Giblin, S., 1995. Infusions of diazepam and allopregnanolone into the midbrain central gray facilitate open-field behavior and sexual receptivity in female rats. Horm. Behav. 29, 279–295.
McNamara, R.K., Skelton, R.W., 1992. Like diazepam, CL 218,872, a selective ligand for the benzodiazepine omega 1 receptor subtype, impairs place learning in the Morris water maze. Psychopharmacology 107, 347–351.
Meert, T.F., 1992. Ritanserin overcomes exploratory inhibition induced by cocaine withdrawal. Behav. Pharmacol. 3, 149–154.
Meert, T.F., Colpaert, F.C., 1986. The shock probe conflict procedure. A new assay responsive to benzodiazepines, barbiturates and related compounds. Psychopharmacology (Berl.) 88, 445–450.
Meert, T.F., Melis, W., Aerts, N., Clincke, G., 1997. Antagonism of meta-chlorophenylpiperazine-induced inhibition of exploratory activity in an emergence procedure, the open field test, in rats. Behav. Pharmacol. 8, 353–363.
Meng, I.D., Drugan, R.C., 1993. Sex differences in open-field behavior in response to the beta-carboline FG 7142 in rats. Physiol. Behav. 54, 701–705.
Miller, L.G., Greenblatt, D.J., Roy, R.B., Gaver, A., Lopez, F., Shader, R.I., 1989a. Chronic benzodiazepine administration: III. Upregulation of gamma-aminobutyric acidA receptor binding and function associated with chronic benzodiazepine antagonist administration. J. Pharmacol. Exp. Ther. 248, 1096–1101.
Miller, L.G., Woolverton, S., Greenblatt, D.J., Lopez, F., Roy, R.B., Shader, R.I., 1989b. Chronic benzodiazepine administration: IV. Rapid development of tolerance and receptor downregulation associated with alprazolam administration. Biochem. Pharmacol. 38, 3773–3777.
Miller, L.G., Galpern, W.R., Greenblatt, D.J., Lumpkin, M., Shader, R.I., 1990. Chronic benzodiazepine administration: VI. A partial agonist produces behavioral effects without tolerance or receptor alterations. J. Pharmacol. Exp. Ther. 254, 33–38.
Misslin, R., Cigrang, M., 1986. Does neophobia necessarily imply fear or anxiety? Behav. Proc. 12, 45–50.
Moreau, J.L., Kilpatrick, G., Jenck, F., 1997. Urocortin, a novel neuropeptide with anxiogenic-like properties. NeuroReport 8, 1697–1701.
Moreira, E.G., Nascimento, N., Rosa, G.J., Vassilieff, V.S., 1996. Crotoxin-induced behavioral effects in rats. Braz. J. Med. Biol. Res. 29, 629–632.
Moreira, E.G., Nascimento, N., Rogero, J.R., Vassilieff, V.S., 2000. Gabaergic-benzodiazepine system is involved in the crotoxin-induced anxiogenic effect. Pharmacol. Biochem. Behav. 65, 7–13.
Moriarty, D.D., 1995. Anxiogenic effects of a beta-carboline on tonic immobility and open field behavior in chickens (*Gallus gallus*). Pharmacol. Biochem. Behav. 51, 795–798.
Nakamura-Palacios, E.M., De Oliveira, R.W., Gomes, C.F., 1999. Effects of diazepam or haloperidol on convulsion and behavioral responses induced by bilateral electrical stimulation in the medial prefrontal cortex. Prog. Neuropsychopharmacol. Biol. Psychiatry 23, 1369–1388.
Nazar, M., Jessa, M., Plaznik, A., 1997. Benzodiazepine–GABAA receptor complex ligands in two models of anxiety. J. Neural. Transm. 104, 733–746.
Nazar, M., Siemiatkowski, M., Czonkowska, A., Sienkiewicz-Jarosz, H., Plaznik, A., 1999a. The role of the hippocampus and 5-HT/GABA

interaction in the central effects of benzodiazepine receptor ligands. J. Neural. Transm. 106, 369–381.

Nazar, M., Siemiatkowski, M., Bidzinski, A., Czlonkowska, A., Sienkiewicz-Jarosz, H., Plaznik, A., 1999b. The influence of serotonin depletion on rat behavior in the Vogel test and brain 3H-zolpidem binding. J. Neural Transm. 106, 355–368.

Nobrega, J.N., Coscina, D.V., 1983. Central injections of the GABA-transaminase inhibitor ethanolamine-*O*-sulfate (EOS): effects on brain [14C]2-deoxy-D-glucose uptake and behavior in rats. Brain Res. 262, 243–252.

Novas, M.L., Wolfman, C., Medina, J.H., De Robertis, E., 1988. Proconvulsant and 'anxiogenic' effects of *n*-butyl beta carboline-3-carboxylate, an endogenous benzodiazepine binding inhibitor from brain. Pharmacol. Biochem. Behav. 30, 331–336.

O'Connor, W.T., Earley, B., Leonard, B.E., 1985. Antidepressant properties of the triazolobenzodiazepines alprazolam and adinazolam: studies on the olfactory bulbectomized rat model of depression. Br. J. Clin. Pharmacol. 19 (Suppl. 1), 49S–56S.

Pähkla, R., Harro, J., Rago, L., 1996. Behavioural effects of pinoline in the rat forced swimming, open field and elevated plus-maze tests. Pharmacol. Res. 34, 73–78.

Panickar, K.S., McNaughton, N., 1991. Comparison of the effects of buspirone and chlordiazepoxide on successive discrimination. Pharmacol. Biochem. Behav. 39 (2), 275–278 (June).

Papp, M., Przegalinski, E., 1989. The 5-HT3 receptor antagonists ICS 205-930 and GR38032F, putative anxiolytic drugs, differ from diazepam in their pharmacological profile. J. Psychopharmacol. 3, 14–20.

Paré, A.M.T., Paré, W.P., Kluczynski, J., 1999. Negative affect and voluntary alcohol consumption in Wistar-Kyoto (WKY) and Sprague-Dawley Rats. Physiol. Behav. 67 (2), 219–225 (15 August).

Plaznik, A., Stefanski, R., Palejko, W., Kostowski, W., 1991. Serotonergic mechanisms in the nucleus accumbens affected by chronic desipramine treatment. Pharmacol. Biochem. Behav. 39, 43–48.

Podhorna, J., Franklin, K.B., 2000. Pontine tegmentum lesions increase anxiety-like behavior in rats: a comparison with anxiety produced by beta-CCE. Pharmacol. Biochem. Behav. 65, 267–273.

Poggioli, R., Vergoni, A.V., Rasori, E., Marrama, D., Bertolini, A., 1992. Behavioral effects of atriopeptin in rats. Neuropeptides 22, 149–154.

Pohorecky, L.A., Roberts, P., 1991. Activity in a modified open-field apparatus: effect of diazepam and prenatal stress. Neurotoxicol. Teratol. 13, 129–133.

Pritchard, G.A., Galpern, W.R., Lumpkin, M., Miller, L.G., 1991. Chronic benzodiazepine administration: VIII. Receptor upregulation produced by chronic exposure to the inverse agonist FG-7142. J. Pharmacol. Exp. Ther. 258, 280–285.

Ramanathan, M., Jaiswal, A.K., Bhattacharya, S.K., 1998. Differential effects of diazepam on anxiety in streptozotocin induced diabetic and non-diabetic rats. Psychopharmacology (Berl.) 135, 361–367.

Ramboz, S., Oosting, R., Amara, D.A., Kung, H.F., Blier, P., Mendelsohn, M., Mann, J.J., Brunner, D., Hen, R., 1998. Serotonin receptor 1A knockout: an animal model of anxiety-related disorder. Proc. Natl. Acad. Sci. U. S. A. 95, 4476–4481.

Reddy, D.S., Kaur, G., Kulkarni, S.K., 1998. Sigma (sigma1) receptor mediated anti-depressant-like effects of neurosteroids in the Porsolt forced swim test. NeuroReport 9, 3069–3073.

Rex, A., Stephens, D.N., Fink, H., 1996. "Anxiolytic" action of diazepam and abecarnil in a modified open field test. Pharmacol. Biochem. Behav. 53, 1005–1111.

Rex, A., Voigt, J.P., Voits, M., Fink, H., 1998. Pharmacological evaluation of a modified open-field test sensitive to anxiolytic drugs. Pharmacol. Biochem. Behav. 59, 677–683.

Rizzi, C.A., Prudentino, A., Giraldo, E., 1993. Effects on general behaviour and neurotransmitter functions of a new 5-hydroxytryptamine3 receptor antagonist with potential therapeutic relevance in central nervous system disturbances. Arzneimittelforschung 43, 1033–1041.

Salvatierra, N.A., Arce, A., 2001. Day-old chicks categorised on latency to peck, exhibit a stable fear pattern until 15 days of age. Appl. Anim. Behav. Sci. 73, 103–116.

Sanger, D.J., Zivkovic, B., 1988. Further behavioural evidence for the selective sedative action of zolpidem. Neuropharmacology 27, 1125–1130.

Schmitt, U., Hiemke, C., 1998. Combination of open field and elevated plus-maze: a suitable test battery to assess strain as well as treatment differences in rat behavior. Prog. Neuropsychopharmacol. Biol. Psychiatry 22, 1197–1215.

Schmitt, U., Hiemke, C., 1999. Effects of GABA-transporter (GAT) inhibitors on rat behaviour in open-field and elevated plus-maze. Behav. Pharmacol. 10, 131–137.

Schmitt, U., Luddens, H., Hiemke, C., 2000. Behavioral effects of GABA(A) receptor stimulation and GABA-transporter inhibition. Pharmacol. Biochem. Behav. 65, 351–356.

Schmitt, U., Luddens, H., Hiemke, C., 2001. Behavioral analysis indicates benzodiazepine-tolerance mediated by the benzodiazepine binding-site at the GABA(A)-receptor. Prog. Neuropsychopharmacol. Biol. Psychiatry 25, 1145–1160.

Semeniuk, T., Jhangri, G.S., Le Melledo, J.M., 2001. Neuroactive steroid levels in patients with generalized anxiety disorder. J. Neuropsychiatry Clin. Neurosci. 13, 396–398.

Seredenin, S.B., Blednov Yu, A., Badyshtov, B.A., Gordey, M.L., Nagovitsina, Y.A., 1990. Pharmacogenetic analysis of mechanisms of emotional stress: effects of benzodiazepines. Ann. Ist. Super. Sanita 26, 81–87.

Sherif, F., Oreland, L., 1994. Effects of chronic treatment with the GABA-transaminase inhibitor vigabatrin on exploratory behaviour in rats. Behav. Brain Res. 63, 11–15.

Sherif, F., Oreland, L., 1995. Effect of the GABA-transaminase inhibitor vigabatrin on exploratory behaviour in socially isolated rats. Behav. Brain Res. 72, 135–140.

Siemiatkowski, M., Sienkiewicz-Jarosz, H., Czlonkowska, A.I., Bidzinski, A., Plaznik, A., 2000. Effects of buspirone, diazepam, and zolpidem on open field behavior, and brain [3H]muscimol binding after buspirone pretreatment. Pharmacol. Biochem. Behav. 66, 645–651.

Silva, M.R., Felicio, L.F., Nasello, A.G., Bernardi, M.M., 1995. Is perinatal picrotoxin anxiogenic? Braz. J. Med. Biol. Res. 28, 663–666.

Singh, Y., Jaiswal, A.K., Singh, M., Bhattacharya, S.K., 1996. Behavioural effects of prenatal diazepam administration on anxiety patterns in rats. Indian J. Exp. Biol. 34, 1095–1099.

Skutella, T., Probst, J.C., Renner, U., Holsboer, F., Behl, C., 1998. Corticotropin-releasing hormone receptor (type I) antisense targeting reduces anxiety. Neuroscience 85, 795–805.

Stefanski, R., Palejko, W., Kostowski, W., Plaznik, A., 1992. The comparison of benzodiazepine derivatives and serotonergic agonists and antagonists in two animal models of anxiety. Neuropharmacology 31, 1251–1258.

Stefanski, R., Palejko, W., Bidzinski, A., Kostowski, W., Plaznik, A., 1993. Serotonergic innervation of the hippocampus and nucleus accumbens septi and the anxiolytic-like action of midazolam and 5-HT1A receptor agonists. Neuropharmacology 32, 977–985.

Stone, E.A., Manavalan, S.J., Yi, Z., Quartermain, D., 1995. Beta adrenoceptor blockade mimics effects of stress on motor activity in mice. Neuropsychopharmacology 12 (1), 65–71 (February).

Stratton, S.C., Beresford, I.J.M., Elliot, P.J., Hagan, R.M., 1993. Behavioural effects of centrally infused tachykinin NK2 receptor agonists and antagonists in rat models of anxiety. J. Psychopharmacol. 7, A11. (Suppl.).

Sutton, R.E., Koob, G.F., Le Moal, M., Rivier, J., Vale, W., 1982. Corticotropin releasing factor produces behavioural activation in rats. Nature 297, 331–333.

Taira, T., Porkka-Heiskanen, T., Korpi, E.R., 1992. Neonatal administration of a GABA-T inhibitor alters central GABAA receptor mechanisms and alcohol drinking in adult rats. Psychopharmacology 109, 191–197.

Taira, T., Uusi-Oukari, M., Korpi, E.R., 1993. Early postnatal treatment

with muscimol transiently alters brain GABAA receptors and open-field behavior in rat. Eur. J. Pharmacol. 230, 307–312.

Takahashi, L.K., Kalin, N.H., 1989. Role of corticotropin-releasing factor in mediating the expression of defensive behavior. In: Blanchard, R.J., Brain, P.F., Blanchard, D.C., Parmigiani, S. (Eds.), Ethoexperimental Approaches to the Study of Behavior. NATO ASI Series. Kluwer Academic Publishing, Kluwer, Dordrecht, Boston, London, pp. 580–594.

Tashma, Z., Raveh, L., Liani, H., Alkalay, D., Givoni, S., Kapon, J., Cohen, G., Alcalay, M., Grauer, E., 2001. Bretazenil, a benzodiazepine receptor partial agonist, as an adjunct in the prophylactic treatment of OP poisoning. J. Appl. Toxicol. 21 (Suppl. 1), S115–S119.

Thomsen, P.H., 2000. Obsessive-complusive disorder: pharmacological treatment. Eur. Child Adolesc. Psychiatry 9, I76–I84 (Suppl.).

Ueki, S., 1987. Behavioral pharmacology of zopiclone. Sleep 10 (Suppl. 1), 1–6.

Ueki, S., Watanabe, S., Yamamoto, T., Shibata, S., Shibata, K., 1984. Behavioral effects of brotizolam, a new thienotriazolodiazepine derivative. Jpn. J. Pharmacol. 35, 287–299.

Ueki, S., Watanabe, S., Fujiwara, M., Yamamoto, T., Shibata, S., Shibata, K., Ohta, H., Sakurai, Y., Iwasaki, K., Liou, S.Y., et al., 1985. Behavioral and electroencephalographic effects of lormetazepam. Nippon Yakurigaku Zasshi 86, 145–163.

Uhlenhuth, E.H., Matuzas, W., Glass, R.M., Easton, C., 1989. Response of panic disorder to fixed doses of alprazolam or imipramine. J. Affect. Disord. 17, 261–270.

Wagstaff, A.J., Cheer, S.M., Matheson, A.J., Ormrod, D., Goa, K.L., 2002a. Paroxetine: an update of its use in psychiatric disorders in adults. Drugs 62, 655–703.

Wagstaff, A.J., Cheer, S.M., Matheson, A.J., Ormrod, D., Goa, K.L., 2002b. Spotlight on paroxetine in psychiatric disorders in adults. CNS Drugs 16, 425–434.

Walsh, R.N., Cummins, R.A., 1976. The open field test: a critical review. Psychol. Bull. 83, 481–504.

Westenberg, H.G., 1996. Developments in the drug treatment of panic disorder: what is the place of the selective serotonin reuptake inhibitors? J. Affect. Disord. 40, 85–93.

Wikinski, S.I., Acosta, G.B., Gravielle, M.C., Bonavita, C.D., Bisagno, V., Fiszer de Plazas, S., Rubio, M.C., 2001. Diazepam fails to potentiate GABA-induced chloride uptake and to produce anxiolytic-like action in aged rats. Pharmacol. Biochem. Behav. 68, 721–727.

Williams, J.H., Meara, J.R., Azmitia, E.C., 1990. Effects of 5,7-dihydroxytryptamine injections in the fornix–fimbria on locomotor activity in photocell cages and the open field. Behav. Brain Res. 40, 37–44.

Wong, P.T., Ong, Y.P., 2001. Acute antidepressant-like and antianxiety-like effects of tryptophan in mice. Pharmacology 62, 151–156.

Wu, H.C., Chen, K.Y., Lee, W.Y., Lee, E.H., 1997. Antisense oligonucleotides to corticotropin-releasing factor impair memory retention and increase exploration in rats. Neuroscience 78, 147–153.

Yerbury, R.E., Cooper, S.J., 1987. The benzodiazepine partial agonists, Ro16-6028 and Ro17-1812, increase palatable food consumption in nondeprived rats. Pharmacol. Biochem. Behav. 28, 427–431.

Zorrilla, E.P., Schulteis, G., Ling, N., Koob, G.F., De Souza, E.B., 1998. Performance-enhancing ffects of corticotropin-releasing factor binding protein ligand inhibitors. Soc. Neurosci. Abstr. 24, 234.6.