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The Vogel conflict test: procedural aspects, γ-aminobutyric acid, glutamate and monoamines

Mark J. Millan*, Mauricette Brocco

Psychopharmacology Department, Institut de Recherches Servier, Centre de Recherches de Croissy, 125 Chemin de Ronde, 78290 Croissy/Seine, Paris, France

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Abstract

A multitude of mechanisms are involved in the control of emotion and in the response to stress. These incorporate mediators/targets as diverse as γ-aminobutyric acid (GABA), excitatory amino acids, monoamines, hormones, neurotrophins and various neuropeptides. Behavioural models are indispensable for characterization of the neuronal substrates underlying their implication in the etiology of anxiety, and of their potential therapeutic pertinence to its management. Of considerable significance in this regard are conflict paradigms in which the influence of drugs upon conditioned (trained) behaviours is examined. For example, the Vogel conflict test, which was introduced some 30 years ago, measures the ability of drugs to release the drinking behaviour of water-deprived rats exposed to a mild aversive stimulus (''punishment''). This model, of which numerous procedural variants are discussed herein, has been widely used in the evaluation of potential anxiolytic agents. In particular, it has been exploited in the characterization of drugs interacting with GABAergic, glutamatergic and monoaminergic networks, the actions of which in the Vogel conflict test are summarized in this article. More recently, the effects of drugs acting at neuropeptide receptors have been examined with this model. It is concluded that the Vogel conflict test is of considerable utility for rapid exploration of the actions of anxiolytic (and anxiogenic) drugs. Indeed, in view of its clinical relevance, broader exploitation of the Vogel conflict test in the identification of novel classes of anxiolytic agents, and in the determination of their mechanisms of action, would prove instructive.

Keywords: Anxiety; Anxiolytic; Anxiogenic; Stress; Limbic system; Benzodiazepine; 5-HT_{1A} receptor

1. Origins and characteristics of the Vogel conflict test

1.1. Conflict procedures for evaluation of anxiolytic agents

Conflict situations, in which a subject experiences two opposing impulses, are a common and clinically relevant feature of many models employed for the detection of anxiolytic agents. For example, in plus-maze and light–dark paradigms based upon natural behaviours, rodents oscillate between the desire to explore a novel—but threatening—environment and the accompanying fear (Treit, 1985, 1994; Rodgers et al., 1997). In contrast to experimental models involving such *spontaneous* (untrained) behaviours, in other conflict procedures, subjects receive a *punishment* (mild electric shock) leading to suppression of a *conditioned* (learned) response for reinforcement (food or water) (Rodgers, 1997). Punishment-based conflict procedures have been employed for over 40 years in the identification and characterization of anxiolytic agents. Though numerous variations have been described, the basic paradigm was introduced by Geller and Seifter, 1960 in which, essentially, rats are trained to lever press for a food reward: during the ''conflict'' component, responses are inhibited by concomitant, mild electric shocks. Anxiolytic properties are deduced for drugs which selectively enhance punished responses in the presence of shock as compared to unpunished responses emitted in its *absence*. Benzodiazepines and barbiturates, clinically effective anxiolytic agents, were initially demonstrated to exert specific anxiolytic properties active in the Geller–Seifter test and, subsequently, many classes of potential anxiolytic agent have been characterized employing this procedure. However, major disadvantages remain: (1) the necessity for long-term (months) and daily training of subjects and (2) their repeated utilization. That is, exposure to drugs may modify the actions of those subsequently evaluated.

* Corresponding author. Tel.: +33-1-55-72-24-25; fax: +33-1-55-72-24-70.
E-mail address: mark.millan@fr.netgrs.com (M.J. Millan).

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1.2. General features of the Vogel conflict test

1.2.1. Procedural aspects

In light of the aforegoing comments, Vogel et al. (1971) developed a novel conflict procedure—the Vogel conflict test—in which male rats were water-deprived for 48 h and, during a test session of 3 min, drinking was punished by a mild but aversive shock delivered via the spout of the bottle every 20 licks. Accordingly, a specific, drug-induced increase in the number of shocks taken (equivalent to water drunk) was considered to reflect anxiolytic properties.

Subsequently, as summarized in Table 1, procedural variants have been introduced in which the severity of the model has generally been limited: for example, in reducing deprivation to 18 h or in permitting access of otherwise water-deprived animals to water for 1 h a day over a 4-day period prior to the test (Millan et al., 1999; Plaznik et al., 1994a). An additional advantage of permitting limited access to water is that the subjects learn to immediately approach the bottle which they will be presented during the test session. An alternative approach for habituation of rats to the bottle consists in its presentation for a limited period in the test cage itself prior to testing (Kennett et al., 1998; Wada and Fukuda, 1991). Moreover, giving subjects limited access to water daily over the training period allows it to be extended for a longer duration, thereby enhancing stability and reproducibility of performance.

Though certain authors have employed a preliminary (‘‘pre-drug’’) session in which subjects showing the most pronounced response suppression are selected, this introduces an element of bias, complicates the model, does not appear to offer any convincing advantages and has not systematically been adopted (Amano et al., 1993; Kataoka et al., 1991; Shimizu et al., 1992).

In line with the original work of Vogel et al. (1971), a comparatively low intensity of shock has generally been utilized to suppress drinking behaviour, and several authors have reduced its magnitude still further: notwithstanding the risk of false positives, a low shock intensity may increase test sensitivity to anxiolytic agents and

Table 1
Procedures modified from the original Vogel conflict test

Strain (weight, g)	Housing	Access to water in home cage	Access to water in test cage	Test Day	Session duration (min)	Shock intensity (mA)	Shock frequency	References
Holtzman (170)	?	0 for 48 h	0	Day 3	3	0.5	1/20th lick	Vogel et al. (1971)
Wistar (250)	Group	0 for 48 h	0	Day 3	5	0.6	1/20th lick	Griebel et al. (1997b)
Wistar (240)	Ind	0 for 48 h	0	Day 3	5	0.5	every bout	Belcheva et al. (1997)
Wistar (260)	Ind	0 for 18 h	0	Day 2	3	0.3	1/20th lick	Brocco et al. (1990)
Hooded Lister (240)	Group	0 for 18 h	0	Day 2	3	0.75	1/5th lick	Higgins et al. (1992)
Hooded Lister (240)	Group	0 for 24 h	0	Day 2	3	0.75	1/5th lick	Jones et al. (1988)
Wistar (280)	Group	1 h/day for 4 days	0	Day 5	3	0.3	1/20th lick	Millan et al. (1999)
Wistar (200)	Ind	1 h/day for 4 days	0	Day 5	15	0.4	4 s every 5 s	Plaznik et al. (1994a,b,c)
Wistar (160)	Group	0 on Day 1	30 s (Day 2)	Day 3	3	1.5	1/20th lick	Wada and Fukuda (1991)
S-D (250)	Group	0 on Day 1; 4 h on Day 2	3 min (Day 2)	Day 3	3	0.25	every 5 s	Kennett et al. (1998)
Wistar (280)	Ind	0 on Day 1; 30 min on Day 2	10 min (Days 1 and 2)	Day 3	5	0.5	every 2 s	Przegaliński et al. (1994b)
S-D (220)	Group	0 on Day 1; 30 min on Day 2	5 min (Days1 and 2)	Day 3	10	0.16	every 2 s	Hjorth et al. (1987a,b)
Wistar (290)	Group	0 on Day 1	12 min (Days 2 and 3)	Day 4	12	0.20	every bout	Möller et al. (1999)
Wistar (200)	Ind	45 min/day: 4 days	15 min/day: 4 days	Day 5	15	0.4	4 s every 5 s	Stefański et al. (1993a)
Wistar (300)	Group	0 on Day 1 20 min on Day 2	5 min Day 2 (selection rats >200 licks)	Day 3	5	0.25	1/20th lick	Ågmo et al. (1995)
S-D (200)	Group	0 on Day 1	3 min on Day 2	Day 3: 2 pun. sess: Predrug and test	3	0.35	1/20th lick	Shimizu et al. (1992)
S-D (300)	Group	0 on Day 1	3 min on Day 2 (selection rats >300 licks)	Day 3: 2 pun. sess: Predrug and test	3	2.0	1/20th lick	Amano et al. (1993)

S-D = Sprague–Dawley; Ind = individually housed; Group = 2–4 rats/cage and pun. sess. = punished session.

enhance the possibility of detecting anxiogenic properties. Test duration has also, in analogy to Vogel et al. (1971), generally been limited to a few (3–5) minutes, with a longer test duration not apparently offering any advantages. Though the frequency of punishment has been defined either ''per lick'', in line with Vogel et al. (1971), or ''per second'', this does not appear to represent a major difference in terms of test performance and subject response.

In distinction to Vogel et al. (1971), who used Holtzman rats, many authors have preferred alternative rat strains in line with their more extensive use in other experimental models. Surprisingly, though it seems likely that rat strain would be an important variable, there has not been a parallel comparison of different strains as concerns the actions of benzodiazepines or other classes of anxiolytic agent in the Vogel conflict test. Interestingly, with one exception (Wada and Fukuda, 1991), all studies have employed rats heavier than those used by Vogel et al. (1971): though the significance of weight has likewise not been systematically evaluated, informal observations in this laboratory suggest that larger animals yield more robust and less variable patterns of data.

Finally, it is well-known that housing plays an important role in modulating emotionality and the response to stress. Curiously, then, in the paper of Vogel et al. (1971), it was not explicitly stated whether rats were isolated or group-housed during water deprivation, and both individually housed and (more often) group-housed subjects have been utilized in subsequent studies.

1.2.2. Specificity of drug actions

One drawback of the Vogel conflict test compared to the Geller–Seifter procedure is the lack of a punished vs. non-punished component which, in the former case, facilitates evaluation of the specificity of drug actions. In any case, in analogy to the Geller–Seifter model and other punishment-based procedures, it should be established for each novel class of agent examined in the Vogel conflict test, that their anxiolytic (or anxiogenic) actions cannot be *purely* attributed to an influence upon water appetite, motor performance, learning or nociceptive thresholds (Pollard and Howard, 1989; Treit, 1985, 1994). This is by no means straightforward inasmuch as *all* classes of anxiolytic agent modify appetite, motor behaviour, cognition *and/or* nociception. Further, though specific control experiments can be undertaken of, for example, potential antinociceptive properties of anxiolytic agents, actions of drugs in conventional algesiometric models, such as the reflexive tail-flick response to noxious thermal stimuli, do not necessarily reflect their influence upon the response to a noxious electrical stimulus employed as punishment in the Vogel conflict test. As a further illustration of the difficulty of such controls, monitoring the influence of drugs upon spontaneous locomotor activity in an open-field apparatus may be informative but does not correspond closely to the motor response necessary to obtain reinforcement in the Vogel procedure. In this light, it is obviously instructive to compare results in the Vogel conflict test to those obtained in other procedures of anxiolytic activity. However, *no* model for the detection of anxiolytic properties is *entirely* independent of *all* the above-mentioned variables.

1.3. The Vogel conflict test in mice

Recently, the Vogel conflict test has been performed in various strains of mice (Umezu, 1999; Van Gaalen and Steckler, 2000): this is of considerable significance in view of the increasing exploitation of genetically modified animals in the search for new anxiolytic agents (Belzung, 2001; Belzung and Griebel, 2001; Lesch, 2001; Weiss et al., 2000; Wood and Toth, 2001). Indeed, in transgenic mice, it is critical to characterize drug actions employing a battery of contrasting and complementary models encompassing different aspects of anxiety.

1.4. Clinical pertinence

In common with other conflict models responsive to benzodiazepines, the Vogel conflict test is of rather broad significance to clinical anxiety (Pollard and Howard, 1989; Rodgers, 1997; Shekhar et al., 2001; Treit, 1985, 1994). Further, the Vogel conflict test appears to be of particular relevance to generalized anxiety disorders, a common, undertreated yet incapacitating disorder which reveals a chronic prognosis and which is frequently co-morbid with depression and other psychiatric states (Culpepper, 2002; Wittchen et al., 2002).

1.5. Multiple mechanisms for the control of anxious states

Of the remarkable diversity of mediators implicated in the pathogenesis and treatment of anxiety (Belzung and Griebel, 2001; Griebel et al., 1999a; Lesch, 2001; Wood and Toth, 2001), GABAergic, glutamatergic and monoaminergic mechanisms have the most extensively been characterized employing the Vogel conflict test: thus, the principle aim of the following paragraphs is to outline their significance in this model in relation to their global influence upon anxious states. In addition, actions of drugs interacting with neuropeptide receptors are outlined. Finally, attention is briefly drawn to numerous, potential anxiolytic mechanisms which have as yet to be examined by use of the Vogel conflict test. To facilitate comprehension of drug actions, basic features of the neurobiology of specific neurotransmitters and their receptors are summarized: notably, their localization, the effects of their genetic manipulation in mice, and their interaction with monoaminergic pathways—of which a hyperactivity is implicated in the induction of anxious states (see below).

2. GABA

2.1. GABAergic pathways

This review logically commences with GABA and GABAergic pathways, the major mode of inhibitory transmission in the central nervous system (CNS). GABAergic signalling is reinforced by benzodiazepines, anxiolytic actions of which remain a sine qua non for the validation of any protocol for the detection of therapeutically relevant, anxiolytic agents (Table 2) (Gorman, 2002).

GABAergic neurons are found throughout corticolimbic regions involved in the modulation of anxious states wherein they exert an inhibitory influence upon the release of many neurotransmitters mediating anxiogenic actions: notably, upon noradrenaline and serotonin (5-HT) derived from the locus coeruleus and raphe nuclei, respectively, though the extent to which a reduction of monoaminergic transmission is implicated in the anxiolytic properties of GABAergic agents remains controversial (File et al., 1992; Möhler et al., 2002; Plaznik et al., 1994a,b; Shekhar et al., 2002; Tao et al., 1996). Indeed, actions of GABA postsynaptic to monoaminergic pathways in the hippocampus, amygdala, nucleus accumbens, lateral septum and periaqueductal grey clearly fulfill a crucial role in the expression of its anxiolytic properties (Möhler et al., 2002; see below). Mice deficient in glutamate decarboxylase (GAD 65), the principle synthetic route to GABA in the CNS, show enhanced anxiety (Kash et al., 1999) and anxiolytic actions in the Vogel conflict test and other conflict models have been demonstrated for: (1) drugs suppressing GABA uptake into neurones and (2) inhibitors of GABA transaminase (a rate-limiting enzyme of GABA transformation into glutamate) (Ågmo et al., 1991; Liljequist and Engel, 1984).

GABA exerts its inhibitory actions via chloride (Cl^-)-permeable, ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. Heteromeric $GABA_C$ receptors (ligand-gated chloride-channels) are not considered herein since no information specifically pertaining to anxious states is currently available (Zhang et al., 2001a).

2.2. $GABA_A$ receptors: benzodiazepines and neurosteroids

2.2.1. $GABA_A$ receptors and their operation

Ionotropic, pentameric $GABA_A$ receptors are found throughout the cortex and limbic system, and in both adrenergic and serotonergic neurones (Celada et al., 2001; Shekhar et al., 2002; Tao et al., 1996): their levels are modified both by anxiety (Goddard et al., 2001) and by anxiolytic agents themselves (Tanay et al., 2001). The majority of corticolimbic sites comprise ternary associations of two α subunits, two β subunits and a single γ_2 subunit—the significance of the four (1, 2, 3 and 5) subtypes of α subunit is indicated below (Fritschy and Möhler, 1995; Möhler et al., 2001, 2002; Pirker et al., 2000). Their activation results in *rapid* neuronal hypopolarization via the opening of Cl^- permeable ion channels. Anxiolytic properties of the $GABA_A$ receptor agonist, muscimol, in the Vogel conflict test upon injection into the dorsal raphe nucleus or lateral septum support a role of $GABA_A$ sites both presynaptic (Celada et al., 2001; Tao et al., 1996; Wirtshafter and Sheppard, 2001) *and* postsynaptic to serotonergic pathways in the expression of anxiolytic properties (Drugan et al., 1986; Higgins et al., 1992).

The operation of $GABA_A$ receptors can be positively modulated by several allosteric sites (Hevers and Lüddens, 1998; MacDonald and Olsen, 1994), including those for barbiturates such as phenobarbital (Amin, 1999), and for a further injectable anesthetic, propofol (Krasowski et al.,

Table 2
Actions of drugs interacting with GABAergic receptors in the Vogel conflict test

Receptor	Activity	Prototypical ligand	Effect	Loci	Sample references
$GABA_{A(B)}$	Transaminase inhibitor	γ acetylen-GABA	+	ND	Ågmo et al. (1991)
$GABA_{A(B)}$	Reuptake inhibitor	SKF100,330	+	ND	Ågmo et al. (1991)
$GABA_A$	AGO	Muscimol	+	Lateral Septum, DRN	Drugan et al. (1986)
	ANT	Picrotoxin	−	ND	Ågmo et al. (1991)
	Inverse AGO	FG7142	−	ND	Mizoule et al. (1985)
	$\alpha_1>\alpha_2=\alpha_3$ AGO	Zolpidem	+	Hippoc, amygdala, DRN	Depoortere et al. (1986)
	BZP AGO	Diazepam	+	Hippoc, amygdala, DRN, Acc	Dekeyne et al. (2000a,b)
	BZP PAG	Bretazenil	+	Hippocampus	Griebel et al. (1999a)
	$\alpha_2=\alpha_3$ AGO, α_1 PAG	SL651,498	+	ND	Griebel et al. (2001)
	Neurosteroid AGO	Allopregnanolone	+	ND	Wieland et al. (1991)
	Neurosteroid ANT	Pregnenolone	IA	NR	Czlonkowska et al. (1999)
	Barbiturate site	Phenobarbital	+	Amygdala	Shibata et al. (1989)
	"Propofol" site	Propofol	+	ND	Matsuo et al. (1997)
$GABA_B$	AGO	Baclofen	+	ND	Ågmo et al. (1991)
	ANT	δ-amino-valeric acid	IA	NR	Shephard et al. (1992)

+ = anxiolytic; − = anxiogenic; IA = inactive; ND = not determined; NR = not relevant; AGO = agonist; PAG = partial agonist; ANT = antagonist; BZP = benzodiazepine; Acc = nucleus accumbens; DRN = dorsal raphe nucleus and Hippoc = hippocampus.
Structures indicated under "Loci" are those for which evidence is available: it should not be inferred that they are the only sites involved.

1998) which elicit pronounced anxiolytic actions in the Vogel conflict test and other procedures (Matsuo et al., 1997; Shibata et al., 1989; Umezu, 1999). However, of particular current interest are those for benzodiazepines (Möhler et al., 2002; Rudolph et al., 1999) and neurosteroids (Falkenstein et al., 2000; Hevers and Lüddens, 1998).

2.2.2. Benzodiazepines

Benzodiazepines act at the juncture of α and γ_2 subunits of GABA receptors to enhance agonist potency, as well as the duration and (in certain cases) intensity of the hyperpolarization which they elicit (MacDonald and Olsen, 1994; Möhler et al., 2002; Stell and Mody, 2002). Robust anxiolytic actions in the Vogel conflict test are consistently seen with conventional agents, such as diazepam, chlordiazepoxide and clorazepate (Barrett and Gleeson, 1991; Flores and Pellón, 2000), as well as with chemically distinct and highly potent triazolams, such as alprazolam (Söderpalm et al., 1989) (Fig. 1). Partial benzodiazepine receptor agonists, such as imidazenil, bretazanil and pagoclone, are also effective anxiolytic agents in this paradigm

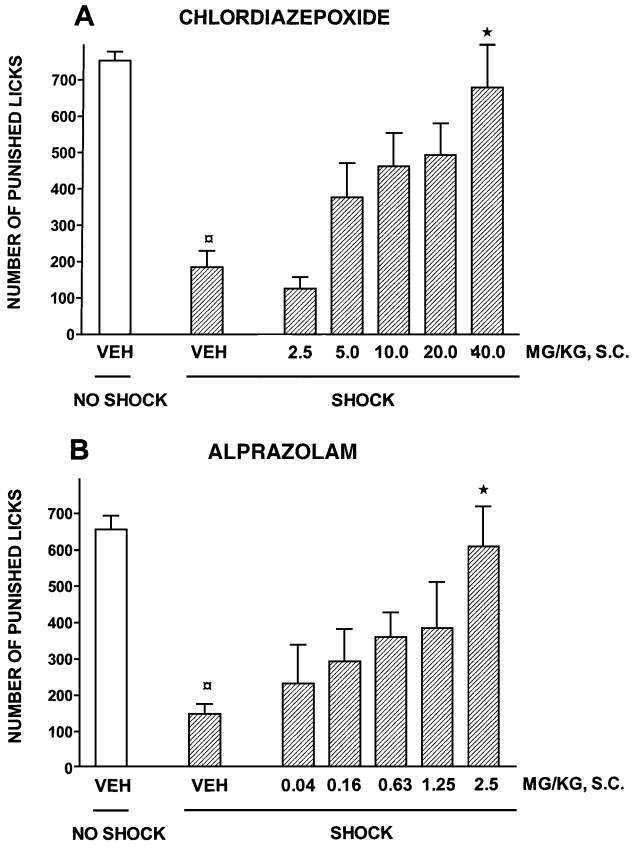

Fig. 1. Actions of the benzodiazepine, chlordiazepoxide, and of the triazolobenzodiazepine, alprazolam, in the Vogel conflict test. The open symbol indicates that, in the presence of punishment, the number of responses emitted is significantly suppressed. Drug treatment is associated with a dose-dependent and significant elevation in responses (*$P<0.05$). Data sources as follows: chlordiazepoxide (Millan et al., 2001) and alprazolam (M. Brocco, unpublished observation).

(Griebel et al., 1999a; Sorbera et al., 2001). Microinjection studies with these and other agents have revealed multiple sites of action in the Vogel conflict test (and other procedures) both at the level of serotonergic cell bodies (implicating an inhibitory influence upon 5-HT release in their actions) and at limbic structures, including the amygdala, hippocampus, lateral septum and nucleus accumbens (Higgins et al., 1988, 1991; Kataoka et al., 1991; Nazar et al., 1999; Shibata et al., 1989; Stefaski et al., 1993a).

Intriguingly, a point mutation (replacement of arginine by a histidine residue) in the α_1 subunit, which is particularly enriched in the cerebellum, basal ganglia, thalamus and cortex (Möhler et al., 2002; Pirker et al., 2000), interfered with the amnesic and sedative actions of diazepam (though not barbiturates), whereas its anxiolytic (and myorelexant) properties were maintained (McKernan et al., 2000; Rudolph et al., 1999). Conversely, genetic disruption of the α_2 subunit, which is concentrated in the cortex and hippocampus (Pirker et al., 2000), suppressed the anxiolytic actions of diazepam—whereas pentobarbital was still effective, again consistent with its interaction with a distinctive site (Amin, 1999). However, elimination of α_3 subunits did not modify the anxiolytic profile of diazepam despite the fact that they are the *only* subtype expressed in serotonergic perikarya (Crestani et al., 2001; Möhler et al., 2002; Pirker et al., 2000). This observation is inconsistent with findings indicating that an inhibitory influence of benzodiazepines upon serotonergic neurones mediates their anxiolytic profile (see further below). Nevertheless, it is possible that the use of mice presenting a different genetic background and of other anxiolytic models—such as the Vogel conflict test—would have yielded an alternative pattern of data. Further, indicative of differences between conclusions of such genetic approaches and pharmacological analyses, the preferential α_1 subunit antagonist, β-carboline-3-carboxylate t-butyl ester, *did* interfere with anxiolytic effects of benzodiazepines in rats (Belzung, 2001; Griebel et al., 1999a,b).

In any case, these important studies of mice possessing disabled $GABA_A$ receptor subunits provide a possible explanation as to why the dose-separation for induction of anxiolytic vs. motor effects—in the Vogel conflict test and other models—is low for zolpidem and zopiclone (Doble, 1999), hypnotics displaying preferential agonist activity at α_1 vs. α_2 subunits (Carlson et al., 2001; Griebel et al., 1999a,b; Stephens et al., 1990; Ueki et al., 1987). Moreover, the modest anxiolytic actions of abecarnil may be a consequence of its weak efficacy at α_2 as compared to α_1 and α_3 subunits (Pribilla et al., 1993), while marked anxiolytic properties of the novel ligand, L838,417 (7-*tert*-butyl-3-(2,5-difluorophenyl)-6(1-methyl-1H-1,2,4-triazol-5-ylmethoxy) [1,2,4]triazolo[4,3-b]pyridazine), in the *absence* of motor sedation, may reflect its agonist properties at α_2, α_3 and α_5, but *not* α_1 sites (McKernan et al., 2000). Finally, SL651,498 (6-fluoro-9-methyl-2-phenyl-4-(pyrrolidin-1-ylcarbonyl)-2,9-dihydro-1*H*-pyrido [3,4-*b*]indol-1-one), a full agonist at α_2 and α_3, but not at α_1 sites, displayed potent

anxiolytic actions in the Vogel conflict test and other models in the relative absence of sedative and amnesic actions (Griebel et al., 2001).

2.2.3. Neurosteroids

Neurosteroids are generated in situ in the brain from cholesterol: they also accumulate and are transformed from endocrine sources. *Non*-genomic actions of neurosteroids lead to rapid alterations in neuronal excitability and reflect—amongst other mechanisms—the modulation of activity at $GABA_A$ receptors (Falkenstein et al., 2000; Lambert et al., 1995; Zinder and Dar, 1999). The term "epalon" was proposed for (endogenous and synthetic) neurosteroids which act via such a GABAergic mechanism, of which the first to be described was the general anesthetic, alphaxolone (Gasior et al., 1999; Lan and Gee, 1997; Vanover et al., 2000). Cerebral pools of cholesterol (primarily glial) are converted via pregnenolone (an *antagonist* at neurosteroid sites) into progesterone, then into its reduced derivatives, allopregnanolone (3 α-hydroxy-5 α-pregnan-20-one) and pregnanolone (or 3 α-hydroxy-5 β-pregnan-20-one). The latter agonists at neurosteroid sites enhance the frequency and duration of opening of the $GABA_A$ receptor-coupled Cl^- channel. The synthesis of neurosteroids is accelerated by stress suggesting recruitment of a counter-regulatory, anxiolytic mechanism (Purdy et al., 1991; Ströhle et al., 2002). Further, it has been speculated that the anxiolytic effects of long-term antidepressant administration (vide infra) involve (independently of 5-HT transporters) an induction of allopregnanolone synthesis (Guidotti and Costa, 1998; Ströhle et al., 2002). Central application of endogenous neurosteroids is associated with anxiolytic properties in the Vogel conflict test (Carboni et al., 1996; Crawley et al., 1986; Czlonkowska et al., 1999; Wieland et al., 1991, 1997), in line with their anxiolytic actions at non-sedative doses in other procedures (Britton et al., 1991; Gasior et al., 1999). Interestingly, their actions appear to complement those of benzodiazepines consistent with an implication of contrasting $GABA_A$ receptor subunits. Indeed, while the significance of α, β and γ receptor subunits to the actions of neurosteroids remains uncertain (Lambert et al., 1995), in contrast to benzodiazepines, genetic disruption of the α_4-subunit of $GABA_A$ receptors, which is well-represented in the hippocampus, interferes with anxiolytic actions of neurosteroids (Wisden et al., 1992; Mihalek et al., 1999).

2.3. $GABA_B$ receptors

In contrast to $GABA_A$ receptors, G protein-coupled $GABA_B$ receptors underlie the *slow* component of central GABAergic inhibition. Though they modulate the activity of adenylyl cyclase, a suppression of activity at voltage-dependent, P/Q and N-type Ca^{2+} channels is implicated in their presynaptic actions at GABAergic terminals and other classes of neurone, while engagement of K^+ channels underlies their hyperpolarizing properties at postsynaptic elements (Billinton et al., 2001). $GABA_B$ receptors, which are heterodimers comprised of two proteins termed $GABA_{B1}$ and $GABA_{B2}$, respectively, are concentrated in the lateral septum, nucleus accumbens, periaqueductal grey, mammillary bodies, hippocampus, amygdala, locus coeruleus and raphe nuclei (Bischoff et al., 1999; Liang et al., 2000; Lu et al., 1999; Margeta-Mitrovic et al., 1999). The inhibitory influence of $GABA_B$ receptors upon the release of NA, glutamate and cholecystokinin (CCK) is consistent with a role in the control of anxious states (Bonanno and Raiteri, 1994; Waldmeier et al., 1994), an assumption supported by their inhibitory influence-together with $GABA_A$ receptors-upon serotonergic cell bodies of raphe nuclei (Varga et al., 2002; Wirtshafter and Sheppard, 2001).

It is, thus, surprising that mice lacking $GABA_B$ receptors do not display alterations in anxiety and that the $GABA_B$ receptor agonist, baclofen, does not invariably elicit anxiolytic actions in rodents (Schuler et al., 2001). This paradox probably reflects the role of $GABA_B$ autoreceptors, activation of which *suppresses* release of GABA onto postsynaptic $GABA_A$ receptors (Andrews and File, 1993; Dalvi and Rodgers, 1996). Nevertheless, baclofen elicited a robust increase in responding in the rat Vogel conflict test (Shephard et al., 1992; Ketelaars et al., 1988).

3. Excitatory amino acids

3.1. Glutamatergic transmisison

Glutamatergic projections of corticolimbic structures play a crucial role, in interaction with GABAergic, monoaminergic and other networks, in the response to stress: correspondingly, glutamatergic mechanisms are implicated in the emotional symptoms of anxious states as well as other psychiatric and neurological disorders (Millan, 2002b; Moghaddam, 2002; Schwendt and Jezová, 2000; Shors et al., 1997). It is, thus, important to consider the actions of drugs interacting with individual classes of ionotropic and metabotropic glutamatergic receptors (Table 3).

3.2. Ionotropic NMDA/glycine$_B$ receptors

For their operation in the mature CNS, heteromeric *N*-methyl-D-aspartate (NMDA) receptors (which consist of two NR1 subunits, and two or three NR2 subunits), require occupation of both a glutamate binding site (on NR2 subunits) and of a "co-agonist" glycine$_B$ (GLY_B) site (on NR1 subunits) (Danysz and Parsons, 1998; Millan, 2002b; Ozawa et al., 1998). The high level of NMDA receptors in the hippocampus, frontal cortex and other limbic regions (op cit.), their reciprocal interaction with monoaminergic pathways (Babar et al., 2001; Millan 2002a,b; Morrow et al., 2000), the similarities in behavioural effects of NMDA receptor antagonists and GABA receptor agonists (Willetts et al., 1990), and functional interactions amongst NMDA

Table 3
Actions of drugs interacting with excitatory amino acid receptors and with nitric oxide synthase in the Vogel conflict test

Receptor	Activity	Prototypical ligand	Effect	Loci	Sample references
NMDA	Recognition Site ANT	CGP37849	+	Hippoc, PAG	Przegaliński et al. (1996)
	OCB	Dizocilpine	+	ND	Jessa et al. (1996)
	GLY_B AGO	Glycine	IA	NR	Chojnacka-Wójcik et al. (1996)
	GLY_B PAG	D-Cycloserine	+	Hippocampus	Klodzińska and Chojnacka-Wójcik (2000)
	GLY_B ANT	5–7 dichloro-kynurenate	+	ND	Plaznik et al. (1994a)
AMPA	ANT	LY326,325	+/IA	ND	Kotlinska and Liljequist (1998b)
MTB	mGluR I (mGlu 5) ANT	MPEP	+	Hippocampus	Tatarczyńska et al. (2001)
	mGluR II AGO	LY354,740	+	Hippocampus	Tatarczyńska et al. (2001)
	mGluR III AGO	L-SOP	+	Hippocampus	Tatarczyńska et al. (2001)
NO	Synthesis Inhibitor	L-NAME	+	ND	Dunn et al. (1995)

OCB = open channel blocker; MTB = metabotropic; NO = nitric oxide; VDCC = voltage-dependent Ca^{2+} channel; MPEP = 2-methyl-6-(phenylethynyl)pyridine and L-SOP = L-serine-*O*-phosphate. For other abbreviations, see Table 2.

receptors and benzodiazepines in the control of anxious states (De Souza et al., 1998; Przegaliński et al., 2000; Sharma and Kulkarni, 1993; Smith and Dudek, 1996), are observations which collectively encourage interest in glutamate recognition site antagonists, open channel blockers (which bind to the cation-permeable channel) and GLY_B receptor ligands as potential anxiolytic agents.

The Vogel conflict test and other conflict paradigms have been successfully used in characterizing anxiolytic properties of glutamate recognition site antagonists and open channel blockers (Bennett and Amrick, 1986; Dunn et al., 1989; Wiley et al., 1998; Willetts et al., 1993). Microinjection studies suggest that they act in the periaqueductal grey and hippocampus, though other structures such as the amygdala may also be implicated (Carobrez et al., 2001; Molchanov and Guimarães, 2002; Plaznik et al., 1994b; Przegaliński et al., 1996; Sajdyk and Shekhar, 1997). Notably, anxiolytic actions of glutamate recognition site antagonists are maintained in the Vogel conflict test and other conflict procedures upon chronic administration (Jessa et al., 1996; Wiley et al., 1992). Several studies have emphasized the specificity of the anxiolytic actions of glutamate recognition site antagonists and open channel blockers in the Vogel conflict test (Jessa et al., 1996; Plaznik et al., 1994b,c; Przegaliński et al., 1996; Wiley et al., 1998). However, a periaqueductal grey microinjection study did not see a clear separation between their modulation of punished responses vs. "non-specific" effects (Molchanov and Guimarães, 2002) and the therapeutic margin for doses displaying anxiolytic actions as compared to those perturbing motor function and eliciting undesirable effects is *low*, in particular for open channel blockers (Danysz and Parsons, 1998; Jessa et al., 1996; Millan, 2002b; Plaznik et al., 1994b; Przegaliński et al., 1996; Wiley et al., 1998).

The latter observation underpins interest in antagonists (and partial agonists) at the GLY_B sites. They have, in fact, produced rather variable results in conflict models, though the balance of evidence suggests significant anxiolytic properties in the *absence* of a generalized disruption of behaviour (Corbett and Dunn, 1991; Danysz and Parsons, 1998; Wiley et al., 1998). Accordingly, several studies documented dose-dependent anxiolytic actions of the partial GLY_B receptor agonists, aminocyclopropyl carboxylic acid and D-cycloserine, in the Vogel conflict test, the effects of which were largely maintained upon long-term administration (Przegaliński et al., 1999; Skolnick et al., 1992). That anxiolytic actions of partial GLY_B receptor agonists reflect a *reduction* in activity at GLY_B sites is suggested by the following observations: (1) GLY_B sites display substantial occupation by endogenous ligands in vivo—and they may even be saturated under conditions of stress (Millan, 2002b); (2) glycine lacks anxiolytic properties in the Vogel conflict test and other conflict procedures (Chojnacka-Wójcik et al., 1996; De Souza et al., 1998; Schmitt et al., 1995); (3) active dose-ranges of D-cycloserine and aminocyclopropyl carboxylic acid in the Vogel conflict test correspond to those at which their antagonist actions are expressed in other models (Danysz and Parsons, 1998); (4) glycine and/or NMDA inhibit the anxiolytic actions of aminocyclopropyl carboxylic acid and D-cycloserine (Klodzińska and Chojnacka-Wójcik, 2000; Teixeira and Carobrez, 1999); (5) mice with genetically disturbed function at GLY_B receptors show reduced anxiety (Kew et al., 2000) and (6) in analogy to open channel blockers and glutamate recognition site antagonists, *pure* GLY_B receptor antagonists manifest anxiolytic properties in several procedures. Such actions have been reported with the Vogel conflict test for 5,7-dichlorokynurenate (Corbett and Dunn, 1991, 1993), upon i.c.v. administration, as well as for the highly selective GLY_B receptor antagonist, L701,324 (7-chloro-4-hydroxy-(3-phenoxy)-phenylquinolin-2[1H]-one) (Kotlinska and Liljequist, 1998a) though, in one study, possibly reflecting a different route of administration or procedural variables, Karcz-Kubicha et al. (1997) failed to demonstrate anxiolytic actions of the latter agent. Paralleling studies of glutamate recognition site antagonists, NMDA receptors in the hippocampus were suggested to mediate the anxiolytic actions of GLY_B receptor partial agonists in the Vogel conflict test, and data from other paradigms suggest that the periaqueductal grey is also involved in their anxiolytic properties (De Souza et al., 1998; Przegaliński et al., 1996).

In line with a functional interelationship between glutamatergic and GABAergic systems in the control of anxious states, the benzodiazepine receptor antagonist, flumazenil, attenuated the anxiolytic actions of the glutamate recognition site antagonist, CGP37849 (D,L-(*E*)-2 amino-4-methylphosphono-3-pentanoic acid), and of the GLY_B receptor partial agonist, aminocyclopropyl carboxylic acid, in the Vogel conflict test—and other procedures (Klodzińska and Chojnacka-Wójcik, 2000; Kuribara et al., 1990; Przegaliński et al., 2000; Sharma and Kulkarni, 1993). The precise substrates underlying such interactions would be of interest to determine, though they presumably reflect (indirect) disinhibition of $GABA_A$ receptors.

3.3. Ionotropic AMPA receptors

Heteromeric, ionotropic α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors (assembled from various combinations of GluR1–4 subunits) are enriched in corticolimbic structures, and are also localized in monoaminergic cell clusters (Lees, 2000; Ozawa et al., 1998). Anxiolytic actions of AMPA receptor antagonists in conflict procedures in both mice and pigeons underpin the potential utility of the Vogel conflict test for evaluation of their anxiolytic potential (Benvenga et al., 1995; Turski et al., 1992). In fact, the AMPA receptor antagonist NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-sulphonamide) was ineffective in a Vogel conflict test in rats, but doses and testing times were not ideal for detection of activity (Czlonkowska et al., 1997). Indeed, Kotlinska and Liljequist (1998b) reported a significant increase in punished responses in a Vogel conflict test with the highly selective AMPA receptor antagonist, LY326,325 ((−)-(3*S*,4aR,6R,8aR)-6-[2-(1*H*-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid), at doses which *failed* to modify locomotor function. Mechanisms underlying anxiolytic actions of AMPA receptor antagonists remain to be elucidated. However, the hippocampus, periaqueductal grey, septum and amygdala are likely sites of action (Matheus and Guimarães, 1997; Menard and Treit, 2000; Sajdyk and Shekhar, 1997). In addition to interactions with GABAergic mechanisms in these structures, AMPA receptor antagonists may exert their anxiolytic properties by suppressing the stress-induced activation of raphe-derived serotonergic and locus coeruleus-derived adrenergic pathways (Fedele et al., 1997; Rasmussen et al., 1996): the latter action may, moreover, account for the inhibitory influence of AMPA receptor antagonists upon benzodiazepine withdrawal (Izzo et al., 2001).

3.4. Metabotropic glutamate receptors

Metabotropic glutamate receptors are functional homodimers (Kunishima et al., 2000) which can be divided into three classes, all of which are found in corticolimbic regions, being particularly prominent in the hippocampus: I (mGlu1 and mGlu5) which are positively coupled to phopspholipase C (PLC), and II and III which are negatively coupled to adenyl cyclase (Bräuner-Osborne et al., 2000; Conn and Pin, 1997; Schoepp et al., 1999). Class II and III receptors localized presynaptically on glutamatergic terminals suppress the release of glutamate, which is known to be enhanced by stress: further, postsynaptic class II and III receptors counter the excitatory actions of co-localized, ionotropic NMDA and AMPA receptors (Karreman and Moghaddam, 1996). On the other hand, excitatory group I receptors presynaptic to glutamatergic pathways are facilitatory to glutamate release and their activation postsynaptically reinforces the depolarizing influence of NMDA and AMPA sites. From this schema, one might anticipate that stimulation of group II/III sites, or blockade of group I sites, would mimic the anxiolytic actions of NMDA and AMPA receptor antagonists. This appears to be the case, based on studies of conflict models of anxiolytic properties (Benvenga et al., 1999; Chojnacka-Wójcik et al., 1996; Helton et al., 1998; Spooren et al., 2000; Tatarczyńska et al., 2001). Indeed, the group II metabotropic glutamate receptor agonist, LY354,740 ((+)2-aminobicyclo[3.1.0]hexane-2,6 dicarboxylic acid), is active in the rat Vogel conflict test upon systemic administration and positive effects of other such agents have been documented upon their introduction into the CA_1 region of the dorsal hippocampus (Tatarczyńska et al., 2001). A group III metabotropic glutamate receptor agonist was similarly active in a rat Vogel conflict test upon injection into this region (Tatarczyńska et al., 2001), a result requiring corroboration with more selective ligands (cf. Chojnacka-Wójcik et al., 1997). Group I metabotropic glutamate receptor antagonists likewise possessed anxiolytic actions in the Vogel conflict test upon systemic or intrahippocampal application (Klodzińska et al., 2000; Tatarczyńska et al., 2001). For all these drugs, anxiolytic actions appear to be specific and not to reflect potential perturbation of cognitive function, motor performance or drinking behaviour (op cit.).

4. Nitric oxide

Nitric oxide (NO) is generated throughout the CNS from L-arginine by the actions of several isoforms of NO synthase (NOS) (Millan, 1999; Wiesinger, 2001): the neuronal form, NOS-1 or nNOS, is enriched in several corticolimbic structures, including the hippocampus and amygdala (Braissant et al., 1999; Egberongbe et al., 1994). It shows a broad pattern of reciprocal interactions with monoaminergic neurones (Millan, 2002a; Segieth et al., 2001; Szabo, 1996). Numerous G-protein coupled receptors modulate the activity of nNOS (Christopoulos and El-Fakahany, 1999), but most interest has focussed on the activation of nNOS by NMDA receptors following an increase in intracellular Ca^{2+} and stimulation of Ca^{2+}-calmodulin (Millan, 1999; Wiesinger, 2001). Indeed, inhibitors of NOS elicit several effects analogous to those of NMDA receptor antagonists (Harkin et al., 1999; Millan, 1999), including anxiolytic

actions in the Vogel conflict test (Dunn et al., 1995). Confirming their specificity, the anxiolytic effects of NOS inhibitors are attenuated by L-arginine (Dunn et al., 1995).

5. Serotonin

5.1. Serotonergic pathways

Serotonergic neurones originating in the median raphe nucleus, which projects to the dorsal hippocampus, septum, accumbens and hypothalamus, and in the dorsal raphe nucleus, which heavily innervates the frontal cortex, ventral hippocampus and amygdala, fulfil a complex and crucial role in the control of various types of anxious state (Table 4) (Baumgarten and Grozdanovic, 1997; Deakin and Graeff, 1991; Graeff et al., 1996). Serotonergic pathways are generally activated by exposure to anxiogenic stimuli and stress, and the Vogel conflict test is accompanied by an increase in 5-HT release in the hippocampus (Adell et al., 1997; Beaufour et al., 2001b; Matsuo et al., 1996; Rueter et al., 1997; Wright et al., 1992). The 5-HT precursor, 5-hydroxytryptophan (5-HTP), displays dose-dependent pro and anticonflict properties in the Vogel conflict test, probably due to the recruitment of different classes of 5-HT receptor (Hjorth et al., 1987a). It provides, thus, an appropriate point of departure for a discussion of the roles of distinct 5-HT receptor types in this procedure (Barrett and Vanover, 1993).

5.2. 5-HT_{1A} receptors

5.2.1. Anti-conflict actions

Inhibitory 5-HT_{1A} autoreceptors are localized on the dendrites of serotonergic cell bodies, while postsynaptic 5-HT_{1A} receptors are enriched in the hippocampus, septum, amygdala, periaqueductal grey, entorhinal cortex and frontal cortex-in the latter structure, they exert a long-loop inhibitory influence upon the raphe (Barnes and Sharp, 1999; Celada et al., 2001; Chopin and Briley, 1987; Olivier et al., 2001). Human volunteers with low levels of 5-HT_{1A} receptors are more likely to be anxious (Tauscher et al., 2001). Further, mice lacking 5-HT_{1A} receptors generally show an anxiogenic phenotype, possibly reflecting deficient activity at postsynaptic 5-HT_{1A} sites inasmuch as 5-HT release does not appear to be modified. Dependent upon the genetic background, the anxiety presented by 5-HT_{1A} knock-out mice may reflect a perturbation in the operation of benzodiazepine/$GABA_A$ receptors (including a down-regulation of α_2 subunits) in the amygdala and hippocampus (File et al., 2000; Griebel, 1999b; Gross et al., 2002; Olivier et al., 2001; Pattij et al., 2002; Sibille and Hen, 2001; Sibille et al., 2000).

In line with these remarks, 5-HT_{1A} receptor partial agonists and agonists evoke anxiolytic actions in conflict models (Barrett, 1992; Chojnacka-Wójcik and Przegaliński, 1991; Hascoët et al., 1994; King et al., 1997; Mansbach et al., 1988; Stanhope and Dourish, 1996). Similarly, numerous studies have shown that 5-HT_{1A} receptor agonists of varying efficacy-though *not*, with one exception, antagonists-are active in the Vogel conflict test in rats (Amano et al., 1993; Barrett, 1992; Dekeyne et al., 2000b; Griebel et al., 2000; Shimizu et al., 1987; Stefański et al., 1992, 1993a; Umezu, 1999; Vanover et al., 1999) (Fig. 2). Paralleling clinical observations, the anticonflict actions of buspirone become progressively more pronounced upon long-term exposure (Schefke et al., 1989). Anxiolytic properties of the novel antipsychotic agent, S16924 ((*R*)-2-{1-[2-(2,3-dihydrobenzo[1,4] dioxin-5-yloxy)-ethyl]-pyrrolidin-3yl}-1-(4-fluorophenyl)-ethanone), in the Vogel conflict test have been attributed to engagement of 5-HT_{1A} receptors (Millan et al., 1999) (Fig. 3).

5.2.2. Significance of pre and postsynaptic 5-HT_{1A} receptors

The respective roles of (pre- and postsynaptic) 5-HT_{1A} receptors in the control of behaviour in the Vogel conflict test and other paradigms is a complex question to which the answer depends upon the model (type of anxiety), serotonergic tone, rearing, test experience, gender, the level of stress,

Table 4
Actions of serotoninergic agents in the Vogel conflict test

Receptor	Activity	Prototypical ligand	Effect	Loci	Sample references
"5-HT"	Precursor	5-Hydroxytryptophan	+	ND	Hjorth et al. (1987a,b)
5-HT_{1A}	AGO	8-OH-DPAT	+	DRN, Hippoc	Engel et al. (1984)
	PAG	Buspirone	+	DRN, Hippoc	Dekeyne et al. (2000b)
	ANT	WAY100,635	IA /+	ND	Dekeyne et al. (2000b)
5-$HT_{1B/D}$	AGO	CGS12066B	IA	ND	Higgins et al. (1992)
	ANT	SB224,289	IA	ND	Brocco, M. (unpub. obs.)
5-HT_{2A}	AGO	DOI	IA	ND	Brocco, M. (unpub. obs.)
	ANT	MDL100,907	+	ND	Brocco, M. (unpub. obs.)
5-HT_{2B}	AGO	BW723C86	+	ND	Kennett et al. (1998)
	ANT	SB215,505	IA	ND	Kennett et al. (1998)
5-HT_{2C}	AGO	Ro-60-0175	IA	ND	Kennett et al. (2000)
	ANT	SB242,084	+	ND	Millan et al. (2001)
5-HT_3	ANT	Ondansetron	IA/+	Hippoc, Acc	Filip et al. (1992)

For abbreviations, see Table 2.

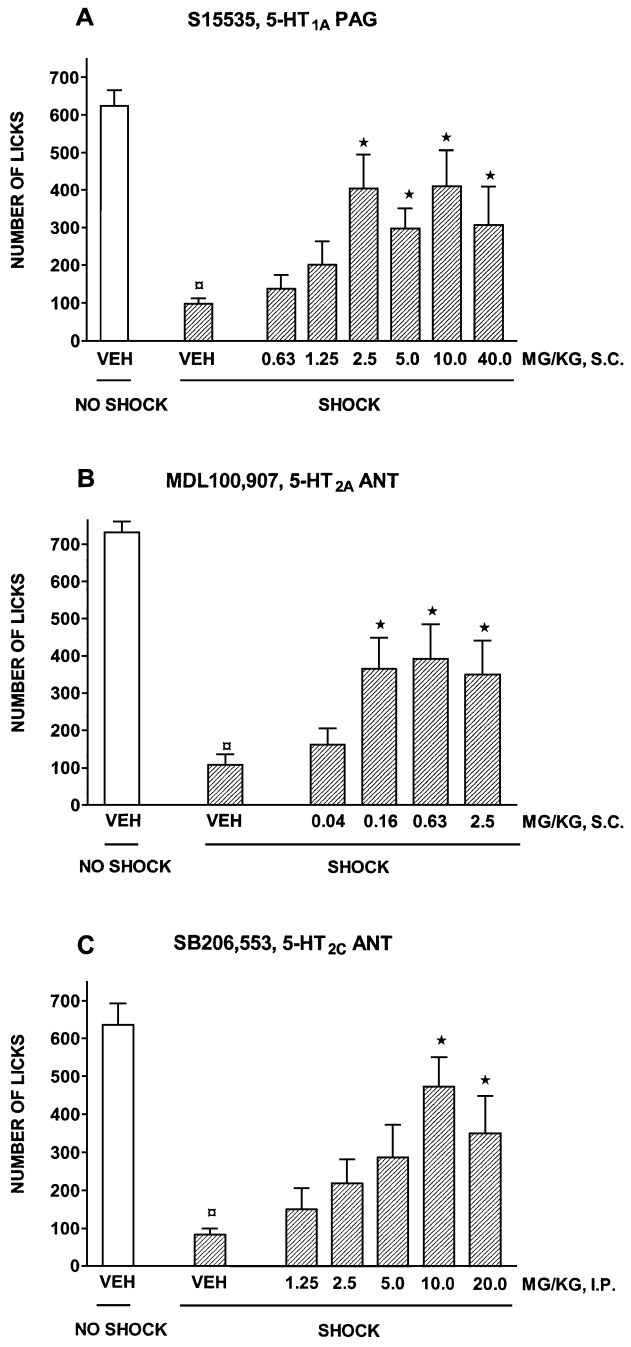

Fig. 2. Actions of serotonergic agents in the Vogel conflict test. S15535 (4-(benzodioxan-5-yl)1-(indan-2-yl)piperazine) is a low efficacy (partial) agonist at 5-HT_{1A} receptors, MDL100,907 (2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol] is a selective antagonist at 5-HT_{2A} receptors and SB206,553 (*N*-3-pyridinyl-3,5 dihydro-5-methylbenzo(1,2-b:4,5-b′)dipyrrole-1(2*H*)carboxamide) is an antagonist at 5-HT_{2C} (and 5-HT_{2B}) receptors. Data sources as follows: S15535 (Dekeyne et al., 2000b); MDL100,907 (M. Brocco, unpublished observation) and SB206,553 (Dekeyne et al., 2000b).

the drug under study as well as its dose, duration and site of administration (Blanchard et al., 1992; Crespi et al., 1992; De Vry, 1995; Menard and Treit, 1999; Olivier et al., 2001).

Many authors argue that engagement of 5-HT_{1A} *autoreceptors* is associated with anxiolytic properties in the Vogel conflict test and other procedures. *First*, local administration of 5-HT_{1A} receptor agonists into the dorsal raphe nucleus and (less prominently) the median raphe nucleus elicits anxiolytic effects (Andrews et al., 1994; Carli and Samanin, 1988; Carli et al., 1989; Cervo et al., 2000; Eison et al., 1986; Higgins et al., 1992; Schreiber and de Vry, 1993). *Second*, parenteral injections of selective 5-HT_{1A} ligands of modest efficacy sufficient to engage pre but *not* postsynaptic populations show pronounced anxiolytic actions even superior to those of full agonists (Cervo et al., 2000; Dekeyne et al., 2000b; De Vry, 1995; Millan et al., 1997; Prezgaliński et al., 1992, 1994b, 1995). *Third*, postsynaptic administration of 5-HT_{1A} receptor agonists into the hippocampus and amygdala can elicit *anxiogenic* actions (Andrews et al., 1994; Gonzalez et al., 1996; Hodges et al., 1987; Nunes-de-Souza et al., 2002). Though such anxiogenic effects have not been seen for the Vogel conflict test, they may reflect activation of 5-HT_{1A} receptors inhibitory to GABAergic neurones in the amygdala and hippocampus (Halasy et al., 1992; Koyama et al., 1999; Matsuyama et al., 1997). *Fourth*, destruction of serotonergic neurones elicits an anxiolytic-like profile in the Vogel conflict test which often interferes with the anxiolytic actions of 5-HT_{1A} receptor agonists (Carli et al., 1989; Cervo and Samanin,

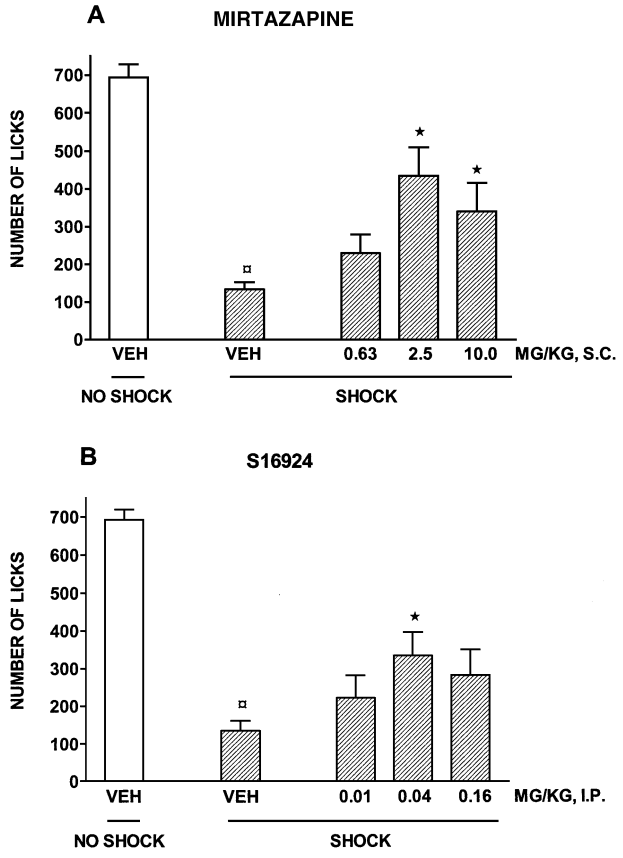

Fig. 3. Actions of the antidepressant agent, mirtazapine, and of the antipsychotic agent, S16924, in the Vogel conflict test. Data sources as follows: mirtazapine (M. Brocco, unpublished observation) and S16924 (Millan et al., 1999).

1995; Eison et al., 1986; Nazar et al., 1999; Schreiber and De Vry, 1993; Söderpalm et al., 1992, 1997). Interestingly, the anxiolytic effects of 5,7-dihydroxytryptamine and 5-HT_{1A} receptor agonists in the Vogel conflict test were susceptible to blockade by $GABA_A$ and benzodiazepine receptor antagonists (Fernóndez-Guasti and López-Rubalcava, 1998; Nazar et al., 1999; Söderpalm and Engel, 1991; Söderpalm et al., 1992, 1997). This indicates that the anxiolytic effects of 5-HT_{1A} autoreceptor stimulation reflect either: (1) the removal of an inhibitory influence of postsynaptic 5-HT_{1A} receptors (or another 5-HT receptor type, such as 5-HT_{1B} sites) upon GABAergic interneurones (see above); (2) release of a positive allosteric modulatory of $GABA_A$ sites, such as neurosteroids (Söderpalm et al., 1997) and/or (3) suppression of the 5-HT_{2C} receptor-mediated interference with GABAergic transmission in the hippocampus (Huidobro-Toro et al., 1996; see below).

Notwithstanding the above comments, studies of the Vogel conflict test (Chojnacka-Wójcik and Przegaliński, 1991; Commissaris et al., 1981; Kataoka et al., 1991; Przegaliński et al., 1992, 1994b; Shimizu et al., 1992; Stefański et al., 1993a) and certain other procedures indicate that microinjection of 5-HT_{1A} receptor agonists into the hippocampus, septum and/or amygdala elicits anxiolytic actions, and that elimination of serotonergic neurones does *not* markedly compromise their actions upon systemic administration (Groenink et al., 2000; Kostowski et al., 1989; Menard and Treit, 1998; Schreiber and De Vry, 1993; Zangrossi et al., 1999). Further, *local* application of 5-HT_{1A} receptor agonists to postsynaptic sites in the periaqueductal grey suppresses aversive effects of periaqueductal grey stimulation (a model of panic-attacks), though systemic administration of 5-HT_{1A} receptor agonists is ineffective, perhaps due to the accompanying acceleration of corticolimbic noradrenaline release (Beckett and Marsden, 1997; Canto-de-Souza et al., 2002; Jenck et al., 1999; Nogueira and Graeff, 1995). A role of postsynaptic 5-HT_{1A} sites in mediating actions of agonists in the Vogel conflict test would be coherent with the interpretation of knock-out studies that a loss of this population underlies the anxiogenic phenotype of mice lacking 5-HT_{1A} receptors (vide supra).

5.2.3. Multiple roles of 5-HT_{1A} receptors

These observations elicit several general comments. *First*, in analogy to benzodiazepines, it is by no means unreasonable that both pre *and* postsynatptic 5-HT_{1A} receptors mediate anxiolytic actions. Engagement of 5-HT_{1A} autoreceptors suppresses serotonergic transmission thereby indirectly relieving the stimulation of anxiogenic, postsynaptic 5-HT_{2C} (and other subtypes of) 5-HT receptor. Inasmuch as postsynaptic 5-HT_{1A} receptors are inhibitory to neuronal activity, their activation interferes with the excitatory actions of co-localized 5-HT_{2C} receptors (Millan et al., 1992). *Second*, 5-HT_{1A} receptors display a complex pattern of reciprocal interactions with GABAergic neurones at both pre and postsynaptic levels: it is, thus, possible that even a single population, such as postsynaptic sites in the hippocampus, both favours (inhibition of GABA release) and suppresses (reinforcement of GABAergic neuronal inhibition) anxious states. *Third*, dependent on serotonergic tone, there may be an optimal degree of efficacy which elicits robust anxiolytic actions by fully and partially engaging pre and postsynaptic sites, respectively. *Fourth*, it is the *global* influence of drugs upon *systemic* administration which is of key significance to their *clinical* utilization.

In this regard, in analogy to the parenteral application of drugs in the Vogel conflict test, buspirone and other 5-HT_{1A} receptor agonists of modest efficacy consistently display anxiolytic activity in patients with generalized anxiety disorders—though their utility alone for treatment of other anxiety conditions remains uncertain (Apter and Allen, 1999; Broocks et al., 2000; Laakman et al., 1998; Oshima et al., 2001; Pecknold, 1997; Rickels et al., 1997). Thus, together with the benzodiazepines, 5-HT_{1A} receptor partial agonists represent the second major class of anxiolytic agents for which their actions in the Vogel conflict test and other conflict models are paralleled by clinical efficacy in man.

5.3. 5-HT_{1B} receptors

Postsynaptic 5-HT_{1B} receptors are localized in the hippocampus, frontal cortex and many other corticolimbic structures, while presynaptic 5-HT_{1B} receptors on serotonergic terminals play a role complementary to dendritic 5-HT_{1A} autoreceptors in the inhibition of 5-HT release (Bruinvels et al., 1994; De Groote et al., 2002; Millan et al., 2000a). It might, thus, be anticipated, that 5-HT_{1B} receptor agonists (which reduce 5-HT release as effectively as 5-HT_{1A} receptor agonists) would mimic the anxiolytic effects of their 5-HT_{1A} counterparts. Remarkably, there is virtually no evidence to support this supposition. Thus, *anxiogenic* actions of 5-HT_{1B} receptor agonists have been seen in paradigms of exploratory behaviour (Lin and Parsons, 2002; Moret and Briley, 2000) while it has been reported that 5-HT_{1B} receptor *antagonists* possess anxiolytic properties (Chopin et al., 1994). Moreover, in the Vogel conflict test, 5-HT_{1B} receptor agonists are ineffective both upon application into the dorsal raphe nucleus and upon systemic administration (Higgins et al., 1992; M. Brocco, unpublished observation). Further, though 5-HT_{1B} receptors were claimed to mediate anxiolytic actions of (mCPP) (1-(3-chlorophenyl) piperazine) in the Vogel conflict test (Chojnacka-Wójcik and Klodzińska, 1992), selective 5-HT_{1B} receptor antagonists were not at that time available, so this interpretation remains questionable. Underpinning these observations, the phenotype of 5-HT_{1B} receptor knockout mice tends towards a *decrease* in anxiety (Belzung, 2001; Malleret et al., 1999; Ramboz et al., 1996; Zhuang et al., 1999). These findings elicit two general comments. *First*, as for 5-HT_{1A} knock-out mice, populations lacking 5-HT_{1B} sites show *no* alterations in 5-HT release, so the influence upon anxious state may largely reflect events *postsynaptic* to serotonergic neurones. *Second*, despite the

historical preoccupation with presynaptic sites, *postsynaptic* 5-HT_{1B} and 5-HT_{1A} receptors may well be of considerable importance. Indeed, in line with recent studies of $GABA_A$ receptor subunits (Möhler et al., 2002; see above), the primordial significance of a suppression of 5-HT release for anxiolytic properties of serotonergic ligands and benzodiazepines should perhaps be reappraised.

5.4. 5-HT_2 receptors

5.4.1. 5-HT_{2A} receptors

Though 5-HT_{2A} receptors are concentrated in entorhinal cortex, amygdala, nucleus accumbens, hippocampus, and are also found in raphe nuclei, the locus coeruleus and the ventrotegmental area, surprisingly little attention has been afforded to their role in the modulation of anxious states (Cornea-Hébert et al., 1999; Lopez-Giménez et al., 1997; Millan, 2002a; Xu and Pandey, 2000). 5-HT_{2A} receptor agonists exert an excitatory influence upon corticolimbic adrenergic and mesocortical dopaminergic pathways: further, they may enhance 5-HT output in the frontal cortex (Liu et al., 2000; Martin-Ruiz et al., 2001; Millan et al., 2000a). In addition, via the protein kinase C (PKC)-mediated phosphorylation of $GABA_A$ receptors, 5-HT_{2A} receptors interfere with the actions of GABA in the frontal cortex (Feng et al., 2001). One might, thus, suspect an *anxiogenic* role of 5-HT_{2A} receptors under certain conditions and, indeed, activation of 5-HT_{2A} receptors facilitates the induction of aversion from the periaqueductal grey (Nogueira and Graeff, 1995). Correspondingly, certain studies have reported anxiolytic actions of selective 5-HT_{2A} receptor antagonists (Graeff et al., 1998; Mora et al., 1997; Motta et al., 1992) including, albeit at relatively high doses, the Vogel conflict test (Griebel et al., 1997a; M. Brocco, unpublished observation) (Fig. 2). Further, the anxiolytic actions of the antipsychotic agent, amperozide, in the Vogel conflict test may reflect its antagonist properties at 5-HT_{2A} receptors (Engel et al., 1989). On the other hand, there is evidence for a *presynaptic*, tonic, excitatory influence of 5-HT_{2A} receptors upon cortical and hippocampal GABAergic neurones (Abi-Saab et al., 1999; Cozzi and Nichols, 1996; Jakab and Goldman-Rakic, 2000; Martin-Ruiz et al., 2001; Shen and Andrade, 1998; Xu and Pandey, 2000). Thus, reports of anxiogenic actions of 5-HT_{2A} receptor antagonists, principally in models of untrained behaviours (Setem et al., 1999), might reflect a *reduction* in GABA release.

The balance of opposing presynaptic (facilitatory) and postsynaptic (inhibitory) influences of 5-HT_{2A} receptors upon GABAergic transmission may, then, account for above-mentioned, contrasting reports of anxiolytic or anxiogenic actions of 5-HT_{2A} receptor antagonists, as well as studies where they proved to be essentially inactive (Gleeson et al., 1989; Griebel et al., 1997a; Setem et al., 1999). Though 5-HT_{2A} receptors may be of lesser significance than their 5-HT_{2C} (see below) counterparts, the balance of evidence supports anxiolytic properties of 5-HT_{2A} receptor antagonists and there is a preliminary report of anxiolytic actions of a selective 5-HT_{2A} receptor antagonist in man (Connell et al., 1995).

5.4.2. 5-HT_{2B} receptors

Though levels of 5-HT_{2B} sites in the central nervous system are low, they have been identified in the amygdala, lateral septum and hypothalamus (Duxon et al., 1997a). In contrast to 5-HT_{2A} and (see below) 5-HT_{2C} sites, anxiolytic actions of the 5-HT_{2B} receptor *agonist*, BW723C86 (α-methyl-5-(2-thienylmethoxy)-1H-indole-3-ethanamine), have been reported in a Vogel conflict test (Duxon et al., 1997b; Kennett et al., 1996a, 1998). 5-HT_{2B} sites in the medial amygdala transduce the actions of BW723C86 in the social interaction test, but the population of 5-HT_{2B} sites mediating its anxiolytic actions in the Vogel conflict test remains to be located (Duxon et al., 1997b).

5.4.3. 5-HT_{2C} receptors

The high density of 5-HT_{2C} receptors in the frontal cortex, hippocampus, amygdala, hypothalamus, periaqueductal grey and septum, provides a solid anatomical foundation for their implication in the control of anxious states (Clemett et al., 2000). 5-HT_{2C} receptors also exist in raphe nuclei suggesting that they modulate serotonergic transmission, though the functional role of this population remains unclear (Barnes and Sharp, 1999; Clemett et al., 2000). In the hippocampus, activation of 5-HT_{2C} receptors, via a Ca^{2+} and PKC-dependent mechanism, interferes with the operation of $GABA_A$ receptors (Huidobro-Toro et al., 1996). This action may be involved in the anxiogenic actions of 5-HT_{2C} receptor agonists which have generally been observed in procedures based on spontaneous behaviours (Gibson et al., 1994; Dekeyne et al., 2000a; Mora et al., 1997; Setem et al., 1999). Moreover, in analogy to other conflict models, selective 5-HT_{2C} receptor antagonists display anxiolytic actions in the Vogel conflict test (Dekeyne et al., 2000a; Gacsalyi et al., 1997; Griebel et al., 1997a; Kennett et al., 1995, 1996b, 1997; Kõks et al., 2001; Martin et al., 1998; Millan et al., 2001; Stefaski et al., 1992; Wood et al., 2001) (Fig. 2). Blockade of 5-HT_{2C} receptors likely accounts for the anxiolytic properties of the antidepressant agents, mianserin and mirtazapine (Fig. 3) (Bjertnaes et al., 1982; Mason et al., 1987; M. Brocco, unpublished observation). The above findings coincide with reports of diminished anxiety in mice lacking 5-HT_{2C} receptors (Heisler et al., 1998a,b). Nevertheless, it should be pointed out that 5-HT_{2C} receptors may *not* fulfil a unitary role in the control of anxious states: for example, populations in the dorsomedial hypothalamus and dorsal periaqueductal grey may inhibit non-conditioned aversive stimuli (Deakin, 1991; Deakin and Graeff, 1991; Graeff et al., 1996; Jenck et al., 1990, 1999; Martin et al., 1998). Indeed, definitive resolution of the therapeutic significance of 5-HT_{2C} receptors to the control of anxiety will only come upon eagerly awaited trials of (selective) 5-HT_{2C} receptor antagonists (Martin et al., 2002).

5.5. 5-HT$_3$ receptors

5-HT$_3$ sites are ligand-gated, cation-permeable, pentameric ion channels (Dubin et al., 1999; Millan, 2002a). They have been visualized in the entorhinal cortex, hippocampus, septum, amygdala and hypothalamus (Doucet et al., 2000; Miquel et al., 2002). One sub-population is localized on GABAergic neurones (Jakab and Goldman-Rakic, 2000; Morales and Bloom, 1997), underlying their facilitatory influence upon GABA release (Diez-Ariza et al., 1998; Ropert and Guy, 1991; Shen and Andrade, 1998). This action is inconsistent with potential anxiolytic actions of 5-HT$_3$ receptor *antagonists*. Indeed, as comprehensively reviewed by Bentley and Barnes (1995) and Olivier et al. (2000), despite positive effects in models based on exploratory behaviour, in conflict paradigms including the Vogel conflict test, the effects of 5-HT$_3$ receptor antagonists are generally modest, drug-dependent, expressed over a limited dose-range and only seen where parameters are adjusted to elicit only a *low* level of response suppression (Artaiz et al., 1995; Filip et al., 1992; Jones et al., 1988; Olivier et al., 2000; Piper et al., 1988; Stefański et al., 1992). Where active, the amygdala, hippocampus and, possibly, the nucleus accumbens have been implicated in the anxiolytic properties of 5-HT$_3$ receptor antagonists (Costall et al., 1989; Higgins et al., 1991; Malgorzata et al., 1992; Stefański et al., 1993b). Notably, this variable and modest activity of 5-HT$_3$ receptor antagonists in the Vogel conflict test and other conflict models resembles their ambivalent efficacy in clinical trials (Olivier et al., 2000).

6. Noradrenaline

6.1. Adrenergic pathways

Adrenergic projections originating in the locus coeruleus and other cell clusters heavily innervate all corticolimbic regions involved in the control of emotivity (Table 5). Correspondingly, the marked activation of adrenergic pathways evoked by diverse anxiogenic stimuli is accompanied by behavioural and autonomic manifestations of fear (Bremner et al., 1996a,b; Charney and Deutch, 1996; McQuade et al., 1999; Schulz et al., 2002; Shekhar et al., 2002; Sullivan et al., 1999; Tanaka et al., 2000). Indeed, the locus coeruleus integrates numerous neurochemically distinct inputs transducing the effects of, and controlling the response to, anxiogenic stimuli (Kawahara et al., 2000; Lapiz et al., 2001; Singewald and Sharp, 2000).

6.2. α_2-Adrenoceptors

6.2.1. α_2-Adrenoceptor agonists

Three subtypes of α_2-adrenoceptors are known, α_{2A}, α_{2B} and α_{2C}, all of which couple negatively to adenyl cyclase (Hieble et al., 1995). Of these, α_{2B}-adrenoceptors are largely restricted to the thalamus, and α_{2C}-adrenoceptors are particularly dense in the basal ganglia. On the other hand, α_{2A}-adrenoceptors are widely distributed in corticolimbic regions and operate as inhibitory α_2-AR autoreceptors on adrenergic neurones and as inhibitory heteroceptors on serotonergic neurones (Hein et al., 1999; Kable et al., 2000; Millan et al., 2000a; Nicholas et al., 1996). In man, anxiolytic properties of α_2-adrenoceptor agonists, such as clonidine, are most pronounced in the peri-operative environment where sedative, haemostabilizing and analgesic actions are also desirable (Ahmed and Takeshita, 1996; Bitsios et al., 1998; Millan, 2002a; Thomson et al., 1998). In the Vogel conflict test, anxiolytic actions of α_2-adrenoceptor agonists have been seen, but they are expressed over a narrow dose-range (Gower and Tricklebank, 1988; La Marca and Dunn, 1994; MacDonald et al., 1988; Millan et al., 2000a,b; Söderpalm, 1989; Söderpalm et al., 1995a,b) paralleling observations in other conflict models (Cole et al., 1995; Fontana et al., 1990; Söderpalm, 1989). These biphasic actions may reflect: (1) anxiogenic actions of high doses mediated via α_1-adrenoceptors (see below); (2) the onset of motor disruption—indeed, the lack of dissociation of anx-

Table 5
Actions of drugs interacting with α/β-adrenoceptors, or with "D$_2$-like" dopamine receptors, in the Vogel conflict test

Receptor	Activity	Prototypical ligand	Effect	Loci	Sample references
α_1-AR	AGO	ST587	IA	NR	Söderpalm and Engel (1990)
	ANT	Prazosin	IA	NR	Przegaliński et al. (1994a,b)
α_2-AR	AGO	S18616	+	ND	Millan et al. (2000b)
	PAG	Clonidine	+	ND	Söderpalm and Engel (1988)
	ANT	Atipamezole	IA	NR	M. Brocco (unpublished observation)
β_2-AR	AGO	Clenbuterol	IA	NR	Söderpalm and Engel (1990)
$\beta_{1/2}$-AR	ANT	Betaxolol	IA	NR	Przegaliński et al. (1994a,b)
$\beta_{1/2}$-AR	ANT	Propranolol	IA	NR	Söderpalm and Engel (1990)
D_1/D_2	AGO	Apomorphine	+	ND	Hjorth et al. (1986)
D_2/D_3	AGO	Quinpirole	+	ND	Siemiatkowski et al. (2000)
D_2/D_3	AGO	S32504	+	ND	M. Brocco (unpublished observation)
D_2/D_3	ANT	Haloperidol	IA	NR	Millan et al. (1999)
$D_3>D_2$	ANT	Nafadotride	+	ND	Rogoz et al. (2000)

Note that anxiolytic properties of the α_2-AR antagonist, yohimbine, and of the $\beta_{1/2}$-AR partial agonist, pindolol, likely reflect direct activation of 5-HT$_{1A}$ receptors (see text). For abbreviations, see Table 2.

iolytic and sedative dose-ranges is unsurprising inasmuch as *both* these actions implicate α_{2A}-adrenoceptors inhibitory to adrenergic and serotonergic pathways (Millan, 2002a); (3) a hitherto-unexplored role of postsynaptic α_2-adrenoceptors or (4) contrasting actions of α_2-adrenoceptor subtypes (see below).

6.2.2. α_2-Adrenoceptor antagonists

The α_2-adrenoceptor antagonist, yohimbine, is well-known to provoke anxiety in man, most strikingly in patients susceptible to panic attacks (Bremner et al., 1996a,b; Charney et al., 1983; Krystal et al., 1992). Such anxiogenic actions are consistent with its pronounced induction of corticolimbic release of noradrenaline and 5-HT (Millan et al., 2000d), though the significance of α_2-adrenoceptor blockade to the anxiogenic actions of yohimbine has been questioned (Cole et al., 1995; Johnston and File, 1988; Redfern and Williams, 1995). Moreover, while anxiogenic actions of yohimbine have been seen in conflict models, most studies, including those of the Vogel conflict test, have reported *anxiolytic* actions (Gower and Tricklebank, 1988; La Marca and Dunn, 1994; Söderpalm and Engel, 1989, 1990; Söderpalm et al., 1995a,b). The most likely explanation for these paradoxical findings is a role of 5-HT_{1A} receptors, at which yohimbine shows agonist properties (Millan et al., 2000d; Söderpalm et al., 1995a,b). A similar explanation likely accounts for the variable actions of other α_2-adrenoceptor antagonists, such as idazoxan (Krystal et al., 1992; Schmidt et al., 1999; Venault et al., 1993) in these procedures (Hieble et al., 1995; Millan et al., 2000a). Indeed, the highly-selective α_2-adrenoceptor antagonists, RX821,002 (2-(2,3-dihydro-2-methoxy-1,4-benzodioxin-2-yl)-4,5-dihydro-1-*H*-imidazole) and atipamezole, do *not* show anxiolytic actions in a Vogel conflict test (M. Brocco, unpublished observation). Irrespective of the underlying reasons, it must be acknowledged that the Vogel conflict test does *not* reveal the clinically pertinent anxiogenic properties of yohimbine, possibly since they are more closely related to a "panic-like"-state than to "generalized" anxiety.

6.2.3. α_2-Adrenoceptor subtypes

Both pharmacological and knock-out strategies support a key role of the α_{2A}-adrenoceptor subtype in the modulation of anxiety (Millan et al., 2000c; Schramm et al., 2001). These findings correspond to its above-mentioned high density in corticolimbic structures (Nicholas et al., 1996), alterations in its levels in the hippocampus, amygdala and periaqueductal grey upon exposure to stress (Nukina et al., 1987; Tejani-Butt et al., 1994) and the suppressive influence of α_{2A}-adrenoceptors upon cerebral and sympathetic release of noradrenaline and upon corticolimbic release of 5-HT (Hein et al., 1999; Kable et al., 2000; Millan et al., 2000b,c). Though α_{2C}-adrenoceptors have been been suggested to, on the contrary, fulfill a "pro-stress" role, their significance in the modulation of anxious states remains to be directly evaluated (Sallinen et al., 1998, 1999; Schramm et al., 2001).

6.3. α_1-Adrenoceptors

Multiple (α_{1A}, α_{1B} and α_{1D}) classes of postsynaptic α_1-adrenoceptor are positively coupled to phospholipase C and they are all localized (albeit with contrasting patterns) in corticolimbic regions (Day et al., 1997; Nicholas et al., 1996). Despite certain reports of anxiolytic actions of α_1-adrenoceptor *antagonists*, they are ineffective in the Vogel conflict test (La Marca and Dunn, 1994; Söderpalm and Engel, 1988, 1990; Söderpalm et al., 1995a). In fact, based on studies with the Vogel conflict test, it has been suggested: (1) that stimulation of α_1-adrenoceptors underlies *anxiogenic* actions of high doses of clonidine and (2) that, in an opposite fashion, activation of α_1-adrenoceptors potentiates the anxiolytic actions of benzodiazepines (Söderpalm and Engel, 1990; Söderpalm et al., 1995a,b). In view of the major influence of α_1-adrenoceptors upon attentional and cognitive processes, their significance to mood disorders and the existence of multiple α_1-adrenoceptors subtypes, their role in the control of anxious states would justify additional clarification (Arnsten, 1997; Aston-Jones et al., 1999; Day et al., 1997; Hieble et al., 1995).

6.4. β-Adrenoceptors

Interest in β-adrenoceptors (of which the three subtypes couple positively to adenyl cyclase) is underpinned by: (1) the high concentration of β_1- and β_2-adrenoceptors in the cortex, amygdala, hippocampus, periaqueductal grey and other limbic regions (Nicholas et al., 1996); (2) the utilization of β-adrenoceptor blockers in the treatment of performance anxiety (Tyrer, 1992); (3) the facilitatory influence of β_1- and β_2-adrenoceptors upon release of noradrenaline and, probably, 5-HT, in the frontal cortex and subcortical structures (Gobert and Millan, 1999; Murugaiah and O'Donnell, 1995; Tsuiki et al., 2000) and (4) the critical role of β-adrenoceptors in the amygdala, hippocampus and frontal cortex in the modulation of emotion and cognition (Huang and Kandel, 1996; Roozendaal et al., 1999; Zhang et al., 2001b). In fact, anxiolytic properties of β-adrenoceptor antagonists *cannot* be demonstrated in conflict paradigms in rodents (Durel et al., 1986; Fontana et al., 1989; Söderpalm and Engel, 1990) and the Vogel conflict test is no exception inasmuch as their systemic and intrahippocampal administration is ineffective (Przegaliński et al., 1994a, 1995). This insensitivity to β-adrenoceptor antagonists may reflect the facts that: (1) β-adrenoceptor antagonists do not themselves modify central adrenergic transmission and (2) their anxiolytic properties in man are largely exerted in the periphery (Durel et al., 1986; Tyrer, 1992). It should be pointed out that anxiolytic properties of the β-adrenoceptor partial agonist, pindolol—which accelerates clinical actions of antidepressant agents (Stein et al., 2001; Ziegenbein et al., 2000)—in the Vogel conflict test are mediated by its agonist properties at 5-HT_{1A} autoreceptors (Cao and

Rodgers, 1997; Gobert and Millan, 1999; Przegaliński et al., 1994a, 1995; Millan et al., 2000d).

7. Dopamine (Table 5)

7.1. Dopaminergic pathways

Mesocortical and mesolimbic dopaminergic pathways, both of which originate in the ventrotegmental area, play an important role in the control of mood. Though they have been most intensely studied within the perspective of depression and schizophrenia, these disorders frequently reveal comorbid anxious symptoms which are also a major feature of Parkinson's disease (Le Moal and Simon, 1991; Penn et al., 1994; Shiba et al., 2000). Both social phobias and panic attacks may be associated with alterations in central dopaminergic transmission (Grant et al., 1998; Mizuki et al., 1997; Pitchot et al., 1992; Roy-Byrne et al., 1986; Schneier et al., 2000; Tiihonen et al., 1997) while, in rodents, fear elicits a (benzodiazepine-reversible) activation of ventrotegmental area-derived dopaminergic pathways to the amygdala (Coco et al., 1992; Greba et al., 2001; Suzuki et al., 2002), nucleus accumbens (Kalivas and Duffy, 1995; McCullough and Salamone, 1992; Pezze et al., 2001) and, most sensitively, frontal cortex (Beaufour et al., 2001a; Broersen et al., 2000).

Dopamine acts via closely related dopamine D_2, D_3 and D_4 receptors, and via closely related dopamine D_1 and D_5 receptors. The current discussion is confined to dopamine D_2 and D_3 sites inasmuch as information concerning dopamine D_4, D_1 and D_5 receptors and the Vogel conflict test is unavailable.

7.2. Dopamine D_2-like receptors

Dopamine "D_2-like" receptors, all of which couple negatively to adenylyl cyclase, comprise dopamine D_2 receptors, dopamine D_3 receptors and dopamine D_4 receptors. Dopamine D_2 receptors are widely distributed throughout the brain, notably in the frontal cortex, nucleus accumbens, amygdala and septum. Though they are only found at lower concentrations, dopamine D_3 sites are, nevertheless, detectable in the nucleus accumbens, hippocampus and hypothalamus (Jackson and Westlind-Danielsson, 1994; Joyce, 2001; Shafer and Levant, 1998). Dopamine D_2 and, less prominantly, dopamine D_3 receptors function as autoreceptors on dopaminergic neurones. There are preliminary reports of anxiolytic actions of dopaminergic receptor agonists in man (Mizuki et al., 1997). The dopamine D_2-like receptor agonists, apomorphine, quinpirole and 3-(3-hydroxyphenyl)-*N*-propylpiperidine (3-PPP), all increase punished responses in the Vogel conflict test (Hjorth et al., 1986, 1987b). Though these agents do not differentiate dopamine D_2, D_3 and D_4 receptors (Joyce, 2001; Vallone et al., 2000), the novel dopamine receptor agonist, S32504 ((+)-*trans*-3,4,4a,5,6,10b-hexahydro-9-carbamoyl-4-propyl-2*H*-naphth[1,2-b]-1,4-oxazine), which is devoid of activity at dopamine D_4 receptors, reproduces their anxiolytic effects in the Vogel conflict test model (M. Brocco, unpublished observation). Further, anxiolytic actions of S32504 are blocked by selective antagonists at dopamine D_2 but *not* D_3 (or D_4) receptors (M.J. Millan, unpublished observation). These data indicate that activation of dopamine D_2 receptors underlies anxiolytic actions of dopamine "D_2-like" receptor agonists: see Gendreau et al. (1998, 2000). Though dopamine D_2 knock-out mice do not show any marked alteration in anxious states, any potential change might be masked by their pronounced reduction of *spontaneous* locomotor behaviour (Sibley, 1999; Waddington et al., 2001). Highly sensitive dopamine D_2 *autoreceptors* in the ventrotegmental area may participate in the anxiolytic properties of dopamine D_2 receptor agonists inasmuch as they are seen at *low* doses (Bartoszyk, 1998; Borowski and Kokkinidis, 1996; Hjorth et al., 1986; Munro and Kokkinidis, 1997; Rogers et al., 2000). This interpretation is consistent with anxiolytic actions in the Vogel conflict test of 3-PPP which, as a low efficacy dopamine receptor partial agonist, preferentially stimulates pre- vs. postsynaptic populations of dopamine D_2 receptors (Hjorth et al., 1987b). However, the precise mechanism of anxiolytic action of dopamine D_2 receptor agonists requires further evaluation and a role of postsynaptic dopamine D_2 sites in the frontal cortex, which are excitatory to GABAergic interneurons, might also be evoked (Espejo, 1997; Grobin and Deutch, 1998; Ravard et al., 1990).

Despite certain reports of *anxiogenic* actions of DA-depletion and dopamine D_2-like receptor antagonists (Espejo, 1997; Timothy et al., 1999), which would be consistent with above-discussed findings, they are inactive in the Vogel conflict test (M. Brocco, unpublished observation; Millan et al., 1999). Moreover, there have also been reports of *anxiolytic* actions of dopamine "D_2-like" receptor antagonists in conflict and other procedures (Cavazzuti et al., 1999; Pich and Samanin, 1986; Rodgers et al., 1994). It is possible then, that blockade of dopamine D_3 receptors underlies such actions. This contention is supported by: (1) the anxiolytic phenotype of dopamine D_3 knock-out mice (Accili et al., 1996; Blednov et al., 2001; Steiner et al., 1998; Vallone et al., 2002); (2) the anxiogenic effects of dopamine D_3 receptor agonists in others models (Gendreau et al., 2000; Kahaya et al., 1996) and (3) anxiolytic actions of preferential dopamine D_3 receptor antagonists in the Vogel conflict test and other procedures (Bartoszyk, 1998; Rodriguez-Arias et al., 1999; Rogoz et al., 2000). However, such findings await corroboration with highly selective antagonists.

8. Neuropeptides

Notwithstanding the crucial importance of GABAergic, glutamatergic and monoaminergic mechanisms, there is

increasing interest in the significance of neuropeptides-with which they reciprocally interact-in the pathogenesis and control of anxious states (Griebel, 1999a). Certain of these mechanisms have been evaluated in the Vogel conflict test, as summarized in Table 6.

Cholecystokinin, which acts via CCK_1 and CCK_2 receptors, is localized throughout the corticolimbic system wherein it interacts with monoaminergic and GABAergic mechanisms (Noble and Roques, 1999; Tanganelli et al., 2001). The actions of CCK are of particular interest inasmuch as CCK_2 receptor agonists possess anxiogenic (panicogenic) actions in animals and in man, though antagonists have *not* proven effective in therapeutic trials (Lines et al., 1995; Singh et al., 1991). Indeed, in analogy to their inconsistent actions in other conflict models, CCK_2 and CCK_1 receptor antagonists are inactive in the Vogel conflict test (Charrier et al., 1995; Costall et al., 1991; Griebel et al., 1997b; Singh et al., 1991). Moreover, mice lacking CCK_2 receptors do not reveal marked changes in anxious behaviour (Daugé et al., 2001).

Corticotropin releasing factor (CRF) and vasopressin fulfil synergistic roles in the induction of hypophyseal secretion of adrenocorticotropic hormone (ACTH) and both play a broader role at the cerebral level in the control of mood and in the etiology of affective disorders (Aguilera and Radadan-Diehl, 2000; Chen et al., 2000; Steckler and Holsboer, 1999). Though a role of CRF_2 sites in the induction of anxiety should not be ignored, pharmacological studies and observations of transgenic mice with altered activity of CRF and CRF_1 receptors demonstrate that activation of CRF_1 sites elicits anxious states: in addition to actions in the amygdala and other limbic structures, engagement of adrenergic pathways may be involved in their induction of anxiety (Steckler and Holsboer, 1999; Karolyi et al., 1999; Sajdyk et al., 1999, Valentino and Van Bockstaele, 2001). Correspondingly, mice lacking CRF_1 receptors fail to show anxiogenic effects of social defeat in a Vogel conflict test (Contarino et al., 1999). Further, CRF itself is anxiogenic in the Vogel conflict test (Britton et al., 1985) while several non-peptidergic CRF_1 antagonists exert robust anxiolytic properties in this procedure (Griebel et al., 1998, 2002b; Millan et al., 2001). Of several types of Vasopressin receptor, $Vasopressin_{1b}$ receptors co-localized with VP itself in the amygdala and hippocampus appear to be involved in the induction of anxious states (Lolait et al., 1995; Hernando et al., 2001; Vaccari et al., 1998) and mice lacking $Vasopressin_{1b}$ may be anxiogenic (Lolait et al., 2000). Correspondingly, a selective $Vasopressin_{1b}$ antagonist was recently shown to possess anxiolytic properties in the Vogel conflict test (Griebel et al., 2002a; Serradeil-Le Gal et al., 2002).

Neuropeptide Y, which exerts its actions via five receptor types, is highly expressed in several corticolimbic structures: it exerts its anxiolytic actions in at least three regions, the amygdala, the dorsolateral septum and the periaqueductal grey (Heilig et al., 1994; Kask et al., 2002). Interestingly, mice overexpressing Neuropeptide Y display an anxiolytic profile in the Vogel conflict test (Palmiter et al., 1998; Thorsell et al., 2000). In addition to its intrinsic anxiolytic actions in the Vogel conflict test, Neuropeptide Y blocks the anxiogenic properties of CRF in this procedure (Britton et al., 1997, 2000; Heilig et al., 1994; Kask et al., 2002). Activation of Neuropeptide Y_1 receptors is primarily involved in these actions. Indeed, there is evidence from the Vogel conflict test and other models that Neuropeptide Y_2 receptors can elicit either anxiogenic or anxiolytic effects from diverse cerebral structures (Heilig et al., 1989; Kask et al., 2002; Sajdyk et al., 2002).

Though corticolimbic pools of galanin, in interaction with adrenergic pathways, certainly play an important role in the modulation of anxious states, their precise role remains uncertain (Bartfai et al., 1992; Millan, 2002a). This probably reflects contrasting actions at specific loci and via distinct (3) subtypes of receptor (Branchek et al., 2000). Indeed, while i.c.v. injection of galanin acted anxiolytically in the Vogel conflict test, its introduction into the amygdala was associated with anxiogenic properties (Bing et al., 1993; Möller et al., 1999).

Finally, glucagon-like peptide 1, cleaved from pre-proglucagon, is enriched in many corticolimbic regions as well as the locus coeruleus and raphe nuclei (Merchenthaler et al., 1999). Suggesting an anxiogenic role, its administration

Table 6
Actions of ligands at neuropeptide receptors and at adenosine receptors, in the Vogel conflict test

Receptor	Activity	Prototypical ligand	Effect	Determined loci	Sample references
CCK_1	ANT	Lorglumide	IA	NR	Griebel et al. (1997b)
CCK_2	ANT	PD135,158	IA	NR	Griebel et al. (1997b)
$CRF_{1(2)}$	$CRF_{1(2)}$ AGO	CRF	–	ND	Britton et al. (1985)
CRF_1	CRF_1 ANT	CP154,526	+	ND	Millan et al. (2001)
VP_{1b}	ANT	SR149,415	+	ND	Griebel et al. (2002a,b)
Galanin	AGO	Galanin	+/–	Amygdala	Bing et al. (1993)
Glucagon-like peptide	AGO	GLP	–	ND	Möller et al. (2002)
Y_1	AGO	NPY	+	ND	Kask et al. (2002)
Y_2	AGO	NPY_{13-36}	IA	NR	Heilig et al. (1989)

CCK = cholecystokinin; CRF = corticotropin-releasing factor; VP = vasopressin; NK = neurokinin and NPY = neuropeptide Y. For other abbreviations, see Table 2.

into the amygdala elicited anxiety in the Vogel conflict test (Möhler et al., 2002).

9. General discussion

9.1. Mechanisms as yet to be evaluated in the Vogel conflict test

Knock-out studies in mice have revealed a surprisingly large number of anxiogenic and anxiolytic phenotypes, suggesting the implication of many unsuspected mechanisms in the control of emotion and anxious states (Belzung and Griebel, 2001; Lesch, 2001). While caution should be exercised in the interpretation of such findings, especially when awaiting confirmation in other genetic lines, there remain numerous, validated mechanisms for the control of anxious states which have not, to date, been examined with the Vogel conflict test (Nikolaus et al., 2000). Several of these are summarized in Table 7 which provides an agenda for future utilization of the Vogel conflict test in the characterization of potential anxiolytic agent.

Table 7
Summary of potential mechanisms for the modulation of anxiety as yet to be evaluated in the Vogel conflict test

Receptor	Endogenous ligand(s)	Primary localization	Receptor influence upon emotivity	Knock-out Phenotype	Relevant receptor-mediated actions
Kainate	Glutamate, Aspartate	Hippocampus, amygdala	Anxiogenic?	Unknown	↑ Glu release
5-HT_4	Serotonin	Hippoc, habenula, LS, amygdala	Anxiogenic?	Unknown	↑ 5-HT release
5-HT_6	Serotonin	Hippocampus, amygdala	Anxiolytic	Anxiogenic	↓ NA release
D_1	Dopamine	FCX, hippocampus, amygdala, acc	Anxiogenic?	No change	Modulates cognitive response to stress
H_1	Histamine	Hippoc, CX, PAG, amygdala, hypothal. DRN, LC,	Anxiogenic	Anxiolytic	↑ NA, 5-HT release
H_3	Histamine	CX, hippocampus, DRN, LC	Anxiolytic	Unknown	↓ Hist, NA, 5-HT release
Musc M_1–M_4	Acetylcholine	FCX, hippocampus, amygdala, hypothalamus	Anxiogenic/ Anxiolytic	Unknown	Site-dependent
Nicotinic	Acetylcholine	Hippocampus, CX, amygdala, LS	Anxiogenic/ Anxiolytic	Anxiogenic (α_4-subunit)	↑ NA, 5-HT, GABA release: site-dependent
PAC1	PACAP	Hippoc, CX, LS, amygdala, hypoth, DRN, LC	Anxiogenic	Anxiolytic	↑ NA release
SST2	Somatostatin	PAG, amygdala, CX, hippocampus, LC	Anxiolytic	Anxiogenic	↓ NA release
CRF_2	CRF	LS, amygdala, hippoc, DRN	Anxiogenic/ Anxiolytic	Anxiogenic/ Anxiolytic	LS, amygdala are key sites of action
AT_1	Angiotensin II	FCX, hippocampus, PAG, amygdala, LC	Anxiogenic	Unknown	ACE inhibitors are anxiolytic
AT_2	Angiotensin II	FCX, amygdala, PAG, DRN, LC	Anxiolytic	Anxiogenic	↓ NA release?
ANP-A	Atrial natriuretic peptide	Hippocampus, LS, amygdala, hypothalamus	Anxiolytic	Unknown	↓ CRF, NA release
ANP-B	C-type natriuretic peptide	Hippocampus, LS	Anxiogenic	Unknown	↑ CRF release
ORL_1	Orphanin FQ (Nociceptin)	PAG, FCX, LS, amygdala, hippoc, hypothal, DRN, LC	Anxiolytic	Anxiogenic (OFQ) No change (ORL_1)	↓ NA, 5-HT release
Y_5	NPY	Hypothalamus, LS, hippocampus, amygdala	Anxiolytic	Unknown	May act in parallel with Y_1 sites
MCH	Melanocyte-concentrating hormone	CX, hippoc, LS, amygdala, DRN, LC	Anxiogenic	Unknown	Modulates 5-HT and NA release?
NK_1	Substance P	Amygdala, hippoc, hypothalamus	Anxiogenic	Anxiolytic/ No change	↑ GABA, (direct) and↓ 5-HT and NA (indirect release)
NK_3	NK B	Acc, CX, LS, hippocampus	Anxiogenic?	Unknown	↑ NA release
A_{2A}	Adenosine	Amygdala, CX, hippocampus, DRN, LC	Anxiolytic?	Anxiogenic	↑ GABA release
CB_1	Cannabinoid	PAG, hippocampus, CX, amygdala	Anxiogenic/ anxiolytic (dose-dep)	Anxiogenic	Modulates CRF, GABA, 5-HT and NA release
Trk B	BDNF	CX, hippoc, LS, PAG, amygdala, DRN, LC	Anxiogenic?	No change (Heterozygote)	↑ NA, 5-HT release
Cytokine	TNFα, IL-1β, etc.	Corticolimbic	Anxiogenic/ Anxiolytic	TNFα, anxiogenic	Modulate 5-HT, NA, GABA and CRF release
Type II GC	Glucocorticoids	Hippoc, LS, amygdala, hypothalamus	Anxiogenic	Anxiolytic	↑ central CRF release?

CX = cortex; CRF = corticotropin-releasing factor; FCX = frontal cortex; LC = locus coeruleus; DRN = dorsal raphe nucleus; LS = lateral septum; ACE = angiotensin converting enzyme; BDNF = brain-derived neurotrophic factor; MA = monoamine; NK = neurokinin; NPY = neuropeptide Y; ORL_1 = orphanin FQ receptor; TNF = Tissue necrosis factor; IL = interleukin; PACAP = pituitary adenyl cyclase activating peptide and PAG = periaqueductal gray. For other abbreviations, see Table 2.

9.2. Other issues requiring further studies

Several other issues would benefit from additional study employing the Vogel conflict test.

First, an obvious question is whether anxiolytic actions of drugs are maintained upon long-term administration, or whether they progressively diminish. This issue is particularly pertinent to agonists. Following discontinuation of long-term administration, it is also necessary to establish whether there is any rebound, withdrawal anxiety. A related question concerns the influence of long-term drug administration upon the subsequent actions of a different drug class (Li et al., 2001). For example, extended pre-exposure to benzodiazepines in man may hinder expression of the anxiolytic properties of 5-HT_{1A} receptor agonists (DeMartinis et al., 2000). Such potential problems should be experimentally addressed in the Vogel conflict test and other models. These issues are of critical importance to: (1) the design of clinical trials; (2) the reciprocal switching of patients to and from novel agents and (3) evaluation of the utility of drugs for replacing benzodiazepines, including suppression of the withdrawal syndrome which ensues upon cessation of their prescription.

Second, as revealed in Tables 2–6, very little is known concerning neuroanatomical substrates and neuronal mechanisms underlying anxiolytic actions in the Vogel conflict test. Microinjection studies, ''regional'' knock-outs (specific CNS structures) and analogous strategies are important in revealing potentially *contrasting* actions of drugs at *multiple* cerebral sites of action, and in providing insights into neuronal mechanisms underlying their influence upon anxious states (Hammack et al., 2002). Sites and mechanisms of drug action can also be clarified by parallel neurochemical studies of regional alterations in transmitter synthesis and release under conditions of the Vogel conflict test.

Third, relatively few studies have modified parameters of the Vogel conflict test in order to render it sensitive to anxiogenic agents: this is important since, in particular where novel mechanisms of action are under exploration and drug actions are not a priori known, it is advantageous that both increases and decreases in anxiety can be revealed.

10. Conclusions

No single procedure can be considered sufficient for evaluation of anxious states and their modulation by anxiolytic agents. Nevertheless, the Vogel conflict test has proven of importance in the characterization of diverse classes of anxiolytic, and there remains considerable scope for its continued and improved application in the identification of novel agents and in the exploration of their mechanism(s) of action. The robust actions of benzodiazepines and 5-HT_{1A} receptor partial agonists in the Vogel conflict test parallel their clinical efficacy in patients; the variable and mediocre effects of 5-HT_3 receptor antagonists in the Vogel conflict test resemble their unconvincing clinical profiles in man, while the inactivity of CCK_2 receptor antagonists mirrors their lack of therapeutic effectiveness. Such observations support the notion that positive results in the Vogel conflict test are of clinical relevance. However, it would be premature to come to any definitive conclusions for the Vogel conflict test (or other models) until results from therapeutic trials of a greater diversity of anxiolytic agents become available. Though actions in the Vogel conflict test appear to be most pertinent to generalized anxiety disorders in man, clinical information concerning drug actions in specific anxious states will also be instructive in more precisely identifying the type of anxiety modelled by the Vogel conflict test and the therapeutic significance of both positive and negative findings with this paradigm.

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