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Characterization of the profile of neurokinin-2 and neurotensin receptor antagonists in the mouse defense test battery

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Abstract

Defensive behaviors of lower mammals confronted with a predatory stimulus provide an appropriate laboratory model for investigating behavior relevant to human emotional disorders. The mouse defense test battery (MDTB) has been developed because it combines many of the aspects of defense. Briefly, it consists of five tests either associated with potential threat (contextual defense) or the actual presence of an approaching threat (a rat). These latter focus on changes in flight, risk assessment and defensive threat and attack behaviors. Investigations with anxiolytic compounds have shown that these defense reactions may be used to differentiate between several classes of anxiolytic drugs. Here we used the MDTB to compare the behavioral profile of the benzodiazepine diazepam with that of neuropeptide receptor antagonists which have been shown to be involved in the modulation of stress response, namely the NK₂ receptor antagonists, SR48968 (0.01–1 mg/kg) and SR144190 (1–10 mg/kg), and the NT₁ receptor antagonist, SR48692 (1–30 mg/kg). Results showed that all compounds decreased defensive threat/attack, but only diazepam and, to a lesser extent, SR48692 significantly modified risk assessment or flight. Further, none of the neuropeptide receptor antagonists modified contextual defense. Overall, the behavioral profile displayed by diazepam and these latter compounds in the MDTB are consistent with an anxiolytic-like action. However, our results suggest that, while NK₂ and NT₁ receptor antagonists may have limited efficacy on anxiety-related responses including cognitive aspects (i.e. risk assessment), they may have a potential against some forms of anxiety disorders which involve adaptative responses to extreme stress stimuli (e.g. direct confrontation with the threat stimulus). © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Anxiety; Benzodiazepines; Defensive behaviors; Mice; Neuropeptide antagonists; Neurokinin-2 receptor; Neurotensin; Stress

1. Introduction

There are few well accepted animal models of psychiatric disorders. However, a number of animal models of anxiety have been proposed, most of which involve exposure of animals to external (e.g. cues previously paired with foot-shock) or internal (e.g. drug states) stimuli which are assumed to be capable of inducing anxiety in humans. The actual measures taken include suppression of previously punished activities, conditioned emotional responses, a range of sonic and ultrasonic vocalizations and social, and exploratory behaviors (for reviews, see Refs. [1–3]). It has been suggested that defensive behaviors of lower mammals to a number of threatening stimuli, including predators, attacking conspecifics, and dangerous objects or situations, may constitute a reliable model for understanding human emotional disorders [4]. Such behaviors can readily be studied in rodents which show a

complete defensive repertoire in response to danger. The rodent defense test batteries measure a full range of specific defensive behaviors either to a discrete, highly discriminable, and present threat source (i.e. a cat or a rat) or to situations closely associated with the potential for danger but not presenting a discrete, clearly dangerous, stimulus. Primary measures taken comprise escape attempts, freezing, risk assessment (RA), defensive sonic vocalization and attack upon forced contact with the threatening stimulus, and flight. The battery has been validated for use in rats [5] and in mice [6].

The question whether the different defensive responses elicited in the MDTB provide different measures of the same state or measure distinct states of defensiveness, fear or anxiety has been approached by performing a factor analysis of the various behavioral defense reactions observed in the battery and by comparing the effects of drugs used in the clinical management of different anxiety disorders (i.e. generalized anxiety disorder (GAD) and panic disorder (PD)). The factor analysis identified four main independent factors related to emotional processes [7].

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Table 1

Effects of various anxiolytic drug treatment on defensive behaviors in the mouse defense test battery. Taken from Refs.[52,55]. (+++ Produced clear effects; ++ produced significant effects; + demonstrated weak effects; (+) effective at high and mostly sedative doses; o ineffective)

Drug	Action-class	Flight	Risk assessment	Defensive aggression	Contextual anxiety
Alprazolam	BZ	+++	+	+++	++
Chlordiazepoxide	BZ	(+)	++	+++	+
Clobazam	BZ	(++)	++	+++	+++
Clonazepam	BZ	+++	+++	+++	+++
Clorazepate	BZ	+	+++	++	+++
Diazepam	BZ	++	+++	+++	+++
Triazolam	BZ	++	+++	+++	+++
Buspirone	5-HT _{1A} agonist	o	o	+++	++
Imipramine	Tricyclic	+++	+	++	++
Fluoxetine	SSRI	+++	+	++	++
Phenelzine	MAO _{AB} inhibitor	++	+	o	+
Befloxadone	MAO _A inhibitor	++	o	o	o
Moclobemide	MAO _A inhibitor	++	o	o	o

Factor 1 included cognitive aspects of defensive behaviors that appear to be related to the process of acquiring and analyzing information in the presence of threatening stimuli (i.e. RA). Flight responses heavily loaded on Factor 2. Several defensive threat/attack reactions (i.e. upright postures and biting) highly loaded on Factor 3, indicating that this factor reflects more affective-orientated defense reactions. Finally, Factor 4, which includes escape attempts in the absence of the rat, relates to contextual defensiveness. Together, this pattern is consistent with the idea that defense reactions of mice exposed to a threat stimulus may relate to different emotional states, and perhaps that they may model different aspects of human anxiety.

To address this hypothesis further, a variety of different clinically effective and marketed anxiolytic agents have been tested in the MDTB. As summarized in Table 1, these compounds generally tend to decrease defensive behaviors. However, it is noteworthy that some responses are specifically or mainly affected by certain drug classes. Thus, benzodiazepines (BZs) decrease RA activities of animals chased by the rat and defensive threat and attack responses, while the 5-HT_{1A} agent buspirone mainly affects contextual defense and defensive threat and attack behaviors. In addition, the tricyclic antidepressant imipramine, the selective 5-HT reuptake inhibitor (SSRI) fluoxetine and the inhibitors of monoamine oxidase (MAO), moclobemide and phenelzine have a clearer impact on flight responses than on other defensive reactions. Taken together, these observations suggest that RA, flight, defensive threat/attack and escape attempts probably reflect different aspects of anxiety-related reactions, thereby confirming the findings from the factor analysis. Although the clinical evidence for a dissociation of GAD and PD, on the basis of drug response, is controversial, there is general agreement that a range of tricyclic antidepressants, SSRIs, IMAO, and some high potency BZs (e.g. alprazolam, clonazepam) are effective against PD. In contrast, drugs used against GAD, such as traditional BZs (e.g. chlordiazepoxide or diazepam) and the 5-HT_{1A} receptor agonist buspirone, are of minimal

utility in the treatment of PD (for recent reviews, see Refs. [8,9]). Taken together with these clinical observations, the above findings with the MDTB suggest that certain defensive behaviors may be considered particularly relevant in modeling specific aspects of anxiety disorders (Fig. 1).

2. Behavioral profile of neuropeptide receptor antagonists in the mouse defense test battery

Although BZs remain the mainstay of drug treatment in anxiety disorders, research in this area has examined the involvement of other neurotransmitter systems over the past two decades. Much attention has been focused on 5-HT neurotransmission and on the investigation of drugs that selectively interact with the 5-HT receptors [10]. However, after extensive research only one direct 5-HT-acting compound has been launched as an anxiolytic agent [11]. As a result, studies involving 5-HT receptor ligands and anxiety behaviors have decreased within the past few years [12]. Nevertheless, the treatment of anxiety disorders remains an active area of research and anxiolytic drug discovery focuses more on the involvement of neuroactive peptides in the modulation of anxiety behaviors. Among these, cholecystokinin and corticotropin-releasing factor have been the most extensively studied, but the involvement of other neuroactive peptides such as neuropeptide Y, tachykinins (substance P, and neurokinin A and B) and neurotensin (NT) has also been examined [13]. Specific and highly potent non-peptide receptor ligands have been discovered and developed for each of these peptides [14]. A few of them have been tested in the MDTB and as will be shown later they yielded behavioral profiles in this procedure that differed from those observed with BZs.

2.1. Tachykinins: effects of NK₂ receptor antagonists

The mammalian tachykinins are a group of neuropeptides that includes substance P, neurokinin A and neurokinin B. The biological actions of tachykinins are mediated via the

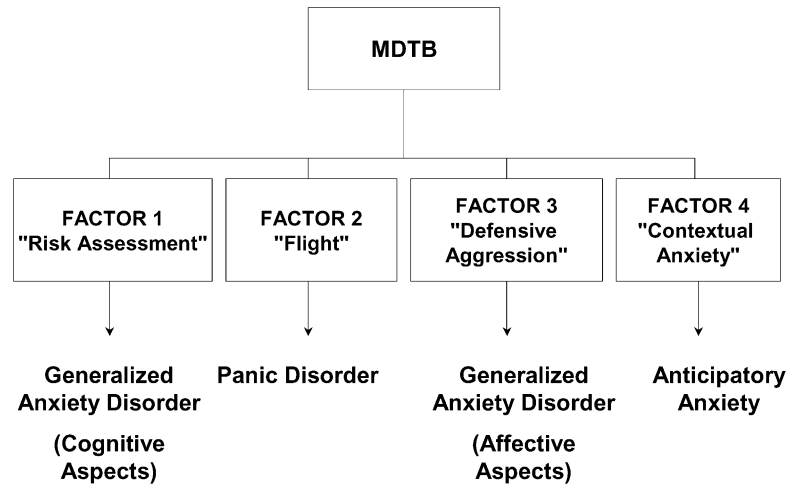


Fig. 1. Tentative view of the clinical relevance of the defensive behaviors measured in the mouse defense test battery.

activation of three G protein-coupled 7-transmembrane (TM) domain receptors designated as NK₁, NK₂ and NK₃ [15]. Both NK₁ and NK₃ receptors are widely distributed in the central nervous system (CNS). The NK₂ receptor is mainly found in smooth muscle of the gastrointestinal, respiratory and urinary tracts, and has also been located in discrete regions of the rodent CNS, including the limbic system, a brain area known to be involved in the modulation of emotional processes [16–20]. The neuroanatomical distribution of NK₂ receptors has prompted speculation about its role in the modulation of emotional processes, and has led to several studies that investigated the behavioral action of NK₂ receptor ligands in animal models of anxiety.

A number of studies in rats have shown that central injection of the preferential NK₂ receptor agonist neurokinin A and the selective NK₂ receptor agonist [β-Ala⁸]neurokinin A-(4–10), a fragment of neurokinin A, produce a

behavioral profile which is consistent with an anxiogenic-like action (for review, see Ref. [13]). Recently, several classes of non-peptide antagonists at NK₂ receptors have been identified [21]. Studies using selective NK₂ receptor antagonists in anxiety models have reported that these compounds display anti-anxiety-like activity in classical models. For example, positive effects have been reported with the selective NK₂ receptor antagonists SR48698 [22–25] and SR144190 (unpublished data) in the light/dark exploration and elevated-plus-maze procedures [22–26]. Moreover, SR48698 significantly increased the time spent by marmosets at the front of the cage following confrontation with a human ‘threat’, an effect which is consistent with an anxiolytic-like action [24]. However, positive effects were not always found as evidenced by a recent study that failed to detect any anxiolytic-like activity of SR48698 in the light/dark test in mice and in two conflict procedures in rats [27]. Moreover, when the anxiolytic-like activity of NK₂ receptor antagonists was directly compared to that of BZs, the magnitude of the anxiety-reducing action of the former was generally smaller, indicating weaker anxiolytic-like potential in these tests.

In the MDTB, SR48698 and SR144190 decreased some flight measures after the rat was placed into the cage and during the chase, but the magnitude of these effects was again less than that of the BZ diazepam (Table 2). During the chase test, SR48698, but not SR144190 reduced, albeit weakly, RA activities (i.e. stops), whereas in the straight alley situation, only diazepam modified significantly this behavior. When contact was forced between threat stimulus and subject in an inescapable straight alley, SR48698 and SR144190 markedly reduced bites to the rat (Fig. 2). Following the removal of the rat from the cage, diazepam, but neither NK₂ receptor antagonist, decreased escape attempts from the test apparatus (Table 2). Overall, the behavioral profile displayed by the NK₂ receptor antagonists in the MDTB is consistent with an anxiolytic-like action. However, while the drug is much less efficient than

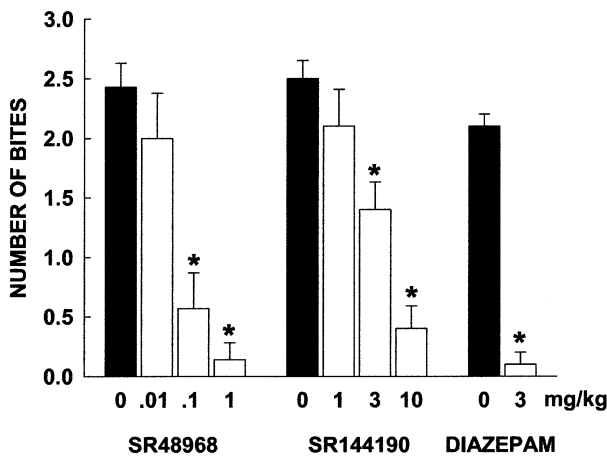


Fig. 2. Effects of two NK₂ receptor antagonists on defensive threat and attack reactions upon forced contact with a hand-held dead Long Evans rat in the mouse defense test battery. Data represent mean ± SEM. **P* < 0.05 compared to vehicle, ANOVA followed by Dunnett's *t*-test. *n* = 11–12.

Table 2

Effects of the NK₂ receptor antagonists SR48698 and SR144490 on several behavioral responses displayed by Swiss mice during (flight and risk assessment) and after (contextual defense) exposure to a Long Evans rat in the MDTB. Data represent mean \pm SEM. * $P < 0.05$ compared to vehicle, ANOVA followed by Dunnett's *t*-test. $n = 11$ – 12

	Dose (mg/kg)	Flight			Risk assessment		Contextual defense
		Avoidance distance (cm)	Avoidance frequency	Chase speed (m/s)	Stops	Approaches–withdrawals	Escape attempts
SR48968 (ip)	0	159.2 \pm 10.5	4.0 \pm 0.4	0.5 \pm 0.1	9.4 \pm 0.2	0.0 \pm 0.0	33.6 \pm 12.7
	0.01	152.9 \pm 13.2	3.1 \pm 0.4	0.6 \pm 0.1	8.9 \pm 0.3	0.0 \pm 0.0	39.0 \pm 14.7
	0.1	83.9 \pm 10.5*	3.0 \pm 0.3	0.7 \pm 0.1	8.0 \pm 0.2*	0.1 \pm 0.1	32.9 \pm 12.4
	1	73.8 \pm 14.4*	1.7 \pm 0.4*	0.7 \pm 0.1	7.9 \pm 0.3*	0.9 \pm 0.3	26.6 \pm 10.0
SR144190 (po)	0	153.5 \pm 9.0	2.8 \pm 0.3	0.8 \pm 0.1	8.6 \pm 0.2	0.5 \pm 0.2	34.5 \pm 10.0
	1	125.2 \pm 14.0	3.2 \pm 0.3	0.7 \pm 0.1	8.3 \pm 0.4	0.9 \pm 0.3	34.1 \pm 10.3
	3	96.6 \pm 13.3*	2.8 \pm 0.3	0.7 \pm 0.1	7.3 \pm 0.5	1.0 \pm 0.3	33.7 \pm 9.7
	10	119.8 \pm 17.3	2.6 \pm 0.4	0.7 \pm 0.1	7.5 \pm 0.7	1.0 \pm 0.3	33.8 \pm 9.7
Diazepam (ip)	0	135.4 \pm 9.4	4.4 \pm 0.2	0.9 \pm 0.1	11.0 \pm 0.3	0.1 \pm 0.1	40.7 \pm 12.9
	3	55.8 \pm 10.2*	0.8 \pm 0.3*	0.5 \pm 0.1*	5.4 \pm 0.4*	1.4 \pm 0.4*	18.0 \pm 5.7*

diazepam on responses which include flight measures and cognitive aspects of defensive behaviors (RA), it appears to be as effective as the BZ on defensive attack, a more 'affective'-orientated defense.

2.2. Neurotensin: effects of the NT₁ receptor antagonist SR48692

Neurotensin is a 13 amino acid peptide originally isolated from bovine hypothalamus by Carraway and Leeman [28]. It displays a wide spectrum of physiological activities, exhibiting a neurotransmitter role in the brain, or behaving as a digestive hormone in the gut and as a regulator of cardiac output and blood pressure in the cardiovascular system [29]. In the brain, NT is a neuromodulator of dopamine transmission [30] and of anterior pituitary hormone secretion [31], and exerts potent hypothermic [32] and analgesic [33] effects. The abundance of NT in the hypothalamus and the central nucleus of the amygdala suggests an important central role for this neuropeptide in the regulation of endocrine responses to external events (e.g. stress) or in the alteration of emotional tone, functions thought to be controlled by the amygdala [34]. Central administration of NT was reported to increase plasma levels of ACTH and corticosterone [35–37]. The activation of the HPA axis by NT has been suggested to be mediated by an enhanced release of CRF from the median eminence to the portal vessels, since pretreatment with the peptide CRF receptor antagonist α -helical CRF_{9–41} attenuated the stimulatory effects of NT [38]. Psychological stressors, such as non-escapable tail electric shock in rats, were found to increase NT mRNA within the medial parvocellular region of the paraventricular nucleus of the hypothalamus [39]. Similarly, cold water swim stress has been shown to increase the expression of NT mRNA in the lateral hypothalamus and medial preoptic regions of the rat brain [40].

The effects of NT are mediated by two G protein-coupled

7-TM domain receptors called NT₁ and NT₂ [41–43]. Recently, a third one, which is structurally different from the NT₁ and NT₂ receptors, has been cloned [44]. Tissue distribution analysis showed that NT₁ receptor expression is most abundant in neurones of the diagonal band of Broca, medial septal nucleus, nucleus basalis magnocellularis, suprachiasmatic nucleus, substantia nigra and ventral tegmental area [45], whereas NT₂ receptor expression is localized in both cortical and sub-cortical structures, notably in the lateral septum, the hippocampal formation and various hypothalamic areas [46,47]. The presence of NT and its receptors in brain regions known to be activated in stress (e.g. amygdala, hypothalamus) has provided the rationale for studying this peptide in animal models of stress-related disorders.

The discovery of the first potent non-peptide NT₁ receptor antagonist, SR48692 [48] has been the starting point of several studies that investigated the neuroendocrine and behavioral actions of NT receptor blockade. SR48692 has been shown to antagonize several behavioral effects observed following central infusion of NT (e.g. turning) [49,50]. Moreover, chronic delivery of SR48692 to the paraventricular nucleus of the hypothalamus via implants was found to attenuate restraint stress-induced elevations in HPA activity [51]. SR48692 was tested in a variety of different classical animal models of anxiety in rodents. However, as shown in Table 3, the drug yielded either weak effects (rat elevated-plus-maze) or was inactive (four-plate test in mice, punished drinking and lever pressing tests in rats, light/dark task in mice). Most of these tests have been pharmacologically validated by BZs, which, as indicated earlier, represent the first-choice treatment in GAD, and it is not clear whether these models are useful when testing compounds which may be effective in other anxiety or stress-related disorders. We therefore tested the effects of SR48692 in the MDTB. Results showed that in the rat avoidance test, SR48692 decreased flight reactions after the rat was introduced into

Table 3

Effects of the NT₁ receptor antagonist SR48692 in several classical animal models of anxiety in rodents. Data represent mean ± SEM. **P* < 0.05 compared to vehicle, ANOVA followed by Dunnett's *t*-test. *n* = 7–16

	Dose (mg/kg, ip)	Elevated-plus-maze (rat)		Punished drinking (rat)	Lever pressing (rat)	Light/dark (mouse)	Four-plate (mouse)
		% Time open arms	Attempts	Shocks received	Punished responding	Time in lit box (s)	Punished crossings
SR48692	0	17.3 ± 4.4	9.3 ± 0.5	12.4 ± 3.1	7 ± 1	11.6 ± 6.4	7.0 ± 0.4
	1	18.1 ± 5.0	6.3 ± 0.9*	10.0 ± 3.8	6 ± 1	14.3 ± 6.4	6.7 ± 0.7
	3	20.3 ± 6.7	6.6 ± 1.0*	15.4 ± 3.5	6 ± 1	6.0 ± 4.7	6.9 ± 1.0
	10	18.7 ± 6.5	5.1 ± 0.8*	13.4 ± 4.6	6 ± 1	9.1 ± 4.5	7.2 ± 0.8

the apparatus, although the magnitude of the effects was less than that of the BZ diazepam (Table 4). During the chase test, SR48692 failed to modify flight speed significantly, but it reduced RA activities (i.e. stops), whereas in the straight alley situation, it increased RA displayed when subjects were constrained in one part of the cage (i.e. approaches followed by withdrawals) (Table 4). As was the case in the rat avoidance test, the magnitude of the effects of SR48692 was generally smaller than that of diazepam.

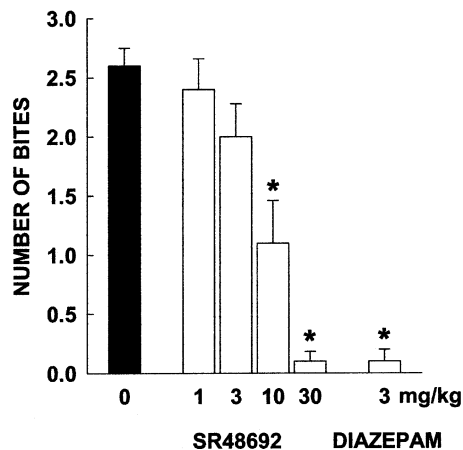


Fig. 3. Effects of the NT₁ receptor antagonist SR48692 on defensive threat and attack reactions upon forced contact with a hand-held dead Long Evans rat in the mouse defense test battery. Data represent mean ± SEM. **P* < 0.05 compared to vehicle, ANOVA followed by Dunnett's *t*-test. *n* = 12.

However, when contact was forced between threat stimulus and subject, SR48692 clearly reduced defensive threat and attack reactions (Fig. 3). Finally, in the post-test, following removal of the rat from the apparatus, SR48692 decreased escape attempts from the test apparatus (Table 4). Together the data from the MDTB confirm that SR48692 has weak or no effects on several behavioral measures primarily modified by BZs. However, they indicate that NT receptor blockade may play a role in the adaptive responses to unavoidable or extreme stress events.

3. Discussion

The earlier MDTB studies have suggested that this laboratory procedure provides a model capable of responding to, and differentiating anxiolytic drugs of different classes through specific profiles of effect on different measures [52]. The use of NK₂ and NT₁ receptor antagonists provided an assessment of the ability of the MDTB and its measures to indicate whether blockade of a particular neuropeptide receptor may be particularly involved in individual defensive behaviors. The main findings with these compounds are summarized in Table 5. It is notable that flight and RA, two sets of behaviors clearly responding to BZs, are only weakly modified by the neuropeptide antagonists, regardless of the receptor involved. Similarly, except the NT₁ receptor antagonist SR48692, the drugs showed minimal efficacy in reducing contextual anxiety, a behavior which is also very sensitive to the action of BZs. In contrast,

Table 4

Effects of the NT₁ receptor antagonist SR48692 on several behavioral responses displayed by Swiss mice during (flight and risk assessment) and after (contextual defense) exposure to a Long Evans rat in the MDTB. The drugs were administered intraperitoneally 30 min before testing. Data represent mean ± SEM. **P* < 0.05 compared to vehicle, ANOVA followed by Dunnett's *t*-test. *n* = 12

	Dose (mg/kg, ip)	Flight			Risk assessment		Contextual defense
		Avoidance distance (cm)	Avoidance frequency	Chase speed (m/s)	Stops	Approaches–withdrawals	Escape attempts
SR48692	0	168.7 ± 4.8	3.6 ± 0.4	0.67 ± 0.1	9.1 ± 0.2	0.1 ± 0.1	35.8 ± 10.3
	1	155.5 ± 8.9	2.6 ± 0.3*	0.70 ± 0.1	8.8 ± 0.1	0.2 ± 0.1	27.0 ± 7.8*
	3	155.1 ± 8.3	2.9 ± 0.3	0.62 ± 0.1	8.6 ± 0.2	0.1 ± 0.1	28.4 ± 8.2*
	10	143.4 ± 8.3*	2.4 ± 0.4*	0.51 ± 0.1	7.6 ± 0.3	0.4 ± 0.3	21.0 ± 6.1*
	30	98.2 ± 6.3*	0.4 ± 0.2*	0.54 ± 0.1	6.4 ± 0.4	0.8 ± 0.3*	18.7 ± 5.4*
Diazepam	3	20.0 ± 0.0*	0.3 ± 0.1*	0.50 ± 0.5*	4.5 ± 0.3*	1.9 ± 0.3*	6.5 ± 1.9*

Table 5

Summary of the effects of various neuropeptide receptor antagonists on defensive behaviors in the MDTB (+++ produced clear effects; ++ produced significant effects; + demonstrated weak effects; o ineffective)

	Action-class	Flight	Risk assessment (RA)	Defensive aggression	Contextual anxiety
Diazepam	BZ	++	+++	+++	+++
SR48968	NK ₂ antagonist	+	+	+++	o
SR144190	NK ₂ antagonist	+	o	+++	o
SR48692	NT ₁ antagonist	+	+	+++	++

all neuropeptide antagonists completely abolished defensive threat and attack reactions, as do BZs. The exact mechanisms underlying the marked effects of these compounds on defensive threat and attack behaviors remain to be determined. In the case of SR48968, the lack of significant effects in the MDTB of its (*R*)-enantiomer, SR48965 [27], which shows only weak affinity for the NK₂ site, indicates that NK₂ receptor blockade may be necessary to produce such effects. Moreover, it has been suggested that NK₂ receptor antagonists may produce some of their *in vivo* effects by interacting with other neurotransmitters such as CRF. For example, Steinberg et al. [53] demonstrated that peripheral administration of SR48968 reduced the increase in neuronal firing of the locus coeruleus and norepinephrine release in the prefrontal cortex both elicited by intraventricular administration of CRF. The site of action of SR48692 is less clear. Although the drug has higher affinity for the NT₁ than for the NT₂ binding site [48], the possibility that this latter receptor may play a role in the effects of SR48692 on defensive behaviors cannot be totally ruled out. In addition, as indicated earlier, there is an interplay between NT and CRF at the level of the paraventricular nucleus of the hypothalamus [37], leading to the possibility that SR48692 may exert its effects on defense via blockade of the increase in HPA activity produced by rat exposure stress. Altogether, these findings point to a central role of CRF in the action of NK₂ and NT₁ receptor antagonists on defensive threat and attack

reactions. This idea is further supported by experiments showing that CRF₁ receptor antagonists produce behavioral effects similar to those of NK₂ and NT₁ receptor antagonists in the MDTB ([54], manuscript in preparation).

A major concern with traditional animal models of anxiety is that they are in most cases unable to discriminate between anxiolysis induced by different classes of drugs, although clinical findings strongly indicate differential therapeutic efficacy profiles of these agents according to the anxiety disorder treated. It is therefore clear that the major advantage of the MDTB is that it provides multiple measures that may be differentially involved in various forms of anxiety. Based on the results from the MDTB with the neuropeptide antagonists, taken in conjunction with those of the reference compounds in this test battery and with the findings from the MDTB factor analysis, we can anticipate potential efficacy of these drugs in the clinical management of a particular anxiety disorder, creating predictions which can be confirmed or disproved by clinical trials involving these compounds (Fig. 4). While BZs have a rather large spectrum of therapeutic activity in anxiety disorders, including cognitive as well as affective-oriented aspects of GAD, anticipatory anxiety and, to a lesser extent, PD, NK₂ and NT₁ receptor antagonists may have more limited efficacy in PD and on cognitive aspects of GAD. However, our data suggest that they may be useful in treating other forms of GAD, especially those

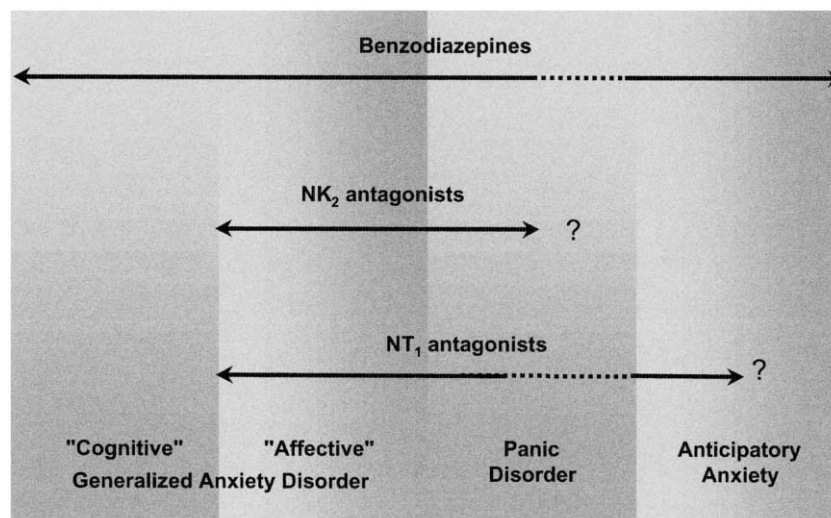


Fig. 4. Schematic view of the expected clinical spectrum of therapeutic activity in anxiety disorders of various neuropeptide receptor antagonists.

in which affective-oriented reactions are the predominant feature.

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