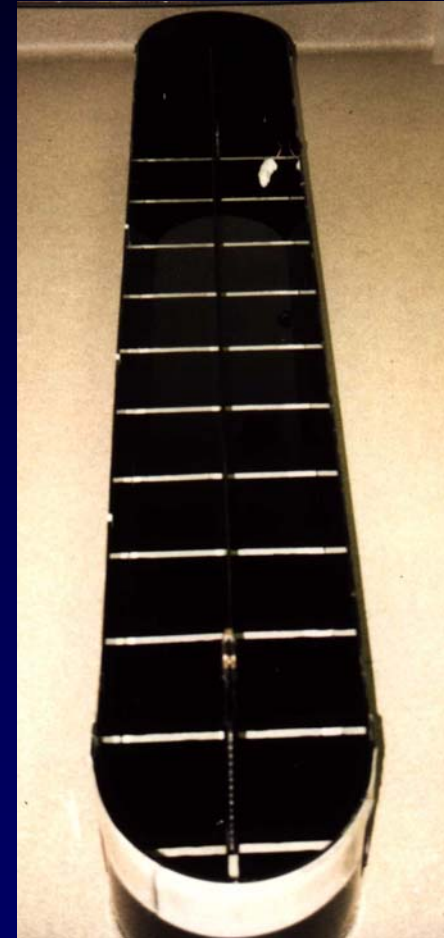


**CHARACTERIZATION OF THE PROFILE
OF NEUROPEPTIDE RECEPTOR ANTAGONISTS
INVOLVED IN THE MODULATION OF STRESS
RESPONSE USING THE MOUSE DEFENSE
TEST BATTERY**

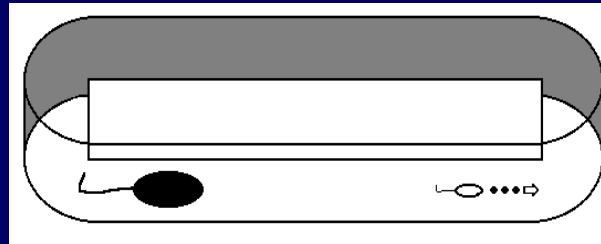
The Mouse Defense Test Battery (MDTB)

- Based on the work of Blanchard and Blanchard on the rat Fear/Defense (F/DTB) and Anxiety/Defense (A/DTB) Test Batteries, which measure defensive behaviors to present and potential threats, respectively
- The MDTB combines many of the features of the F/DTB and A/DTB into a single procedure, eliciting and measuring reactions to both present and anticipated threat (a rat)

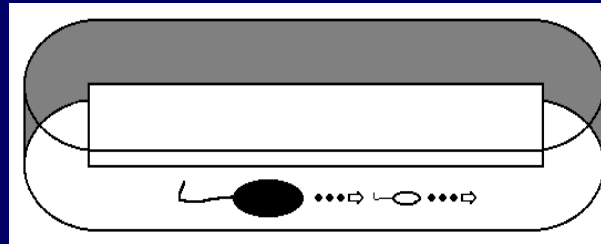


The Mouse Defense Test Battery

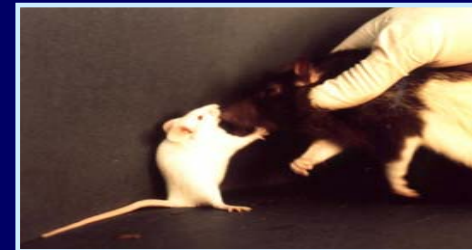
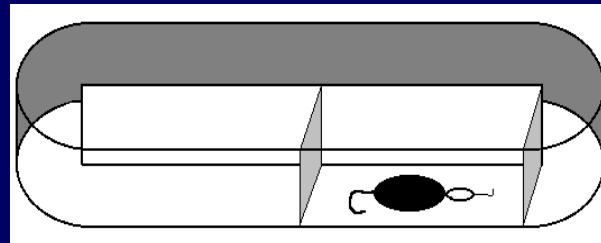
FLIGHT



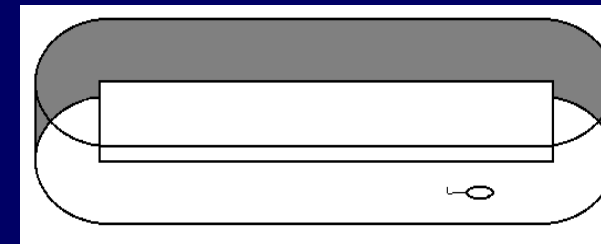
**RISK
ASSESSMENT**



**DEFENSIVE
AGGRESSION**

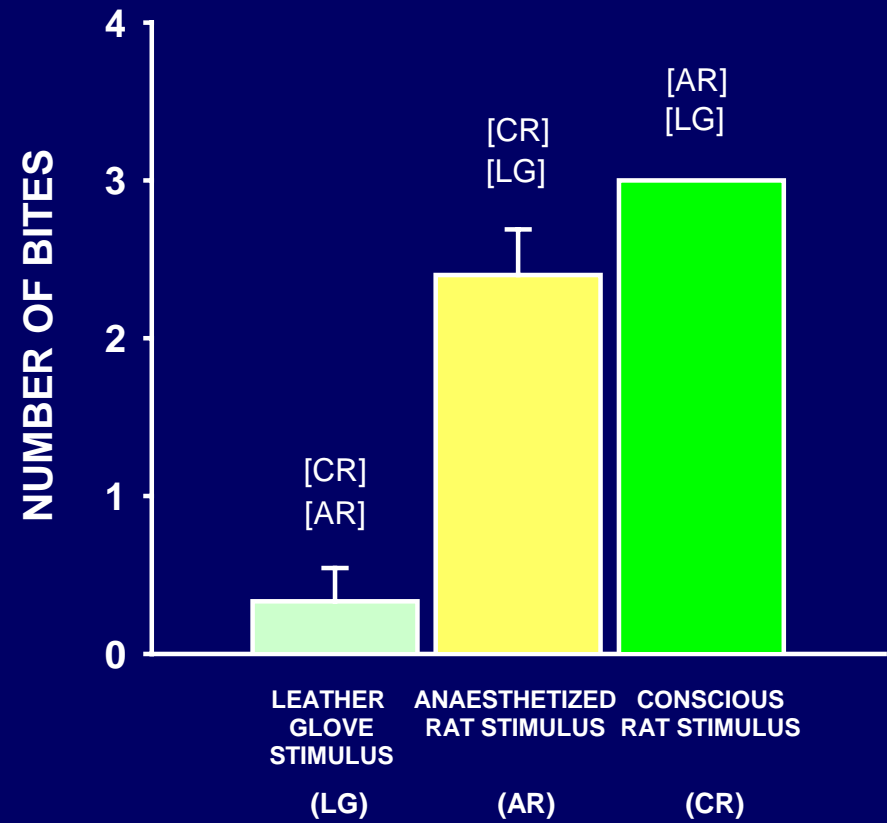
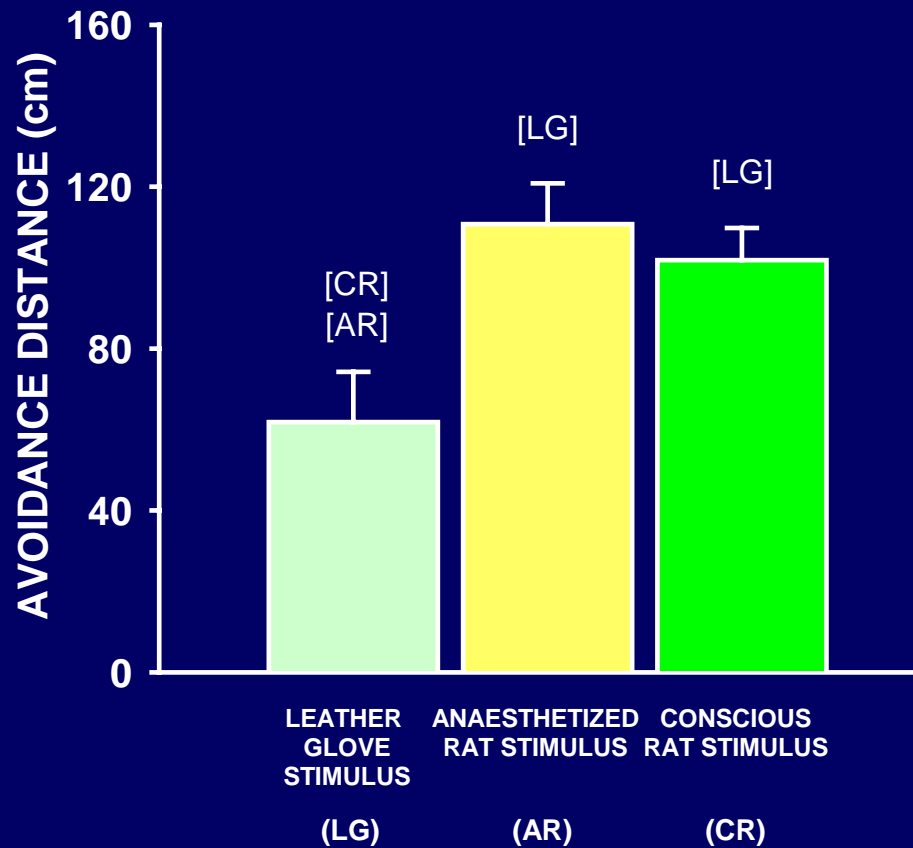


**CONTEXTUAL
ANXIETY**

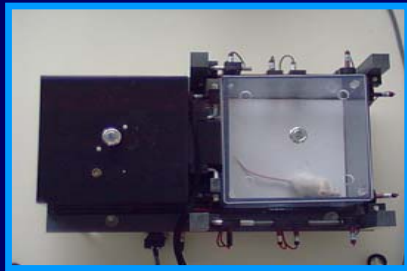


MDTB

Effects of Various Threat Stimuli



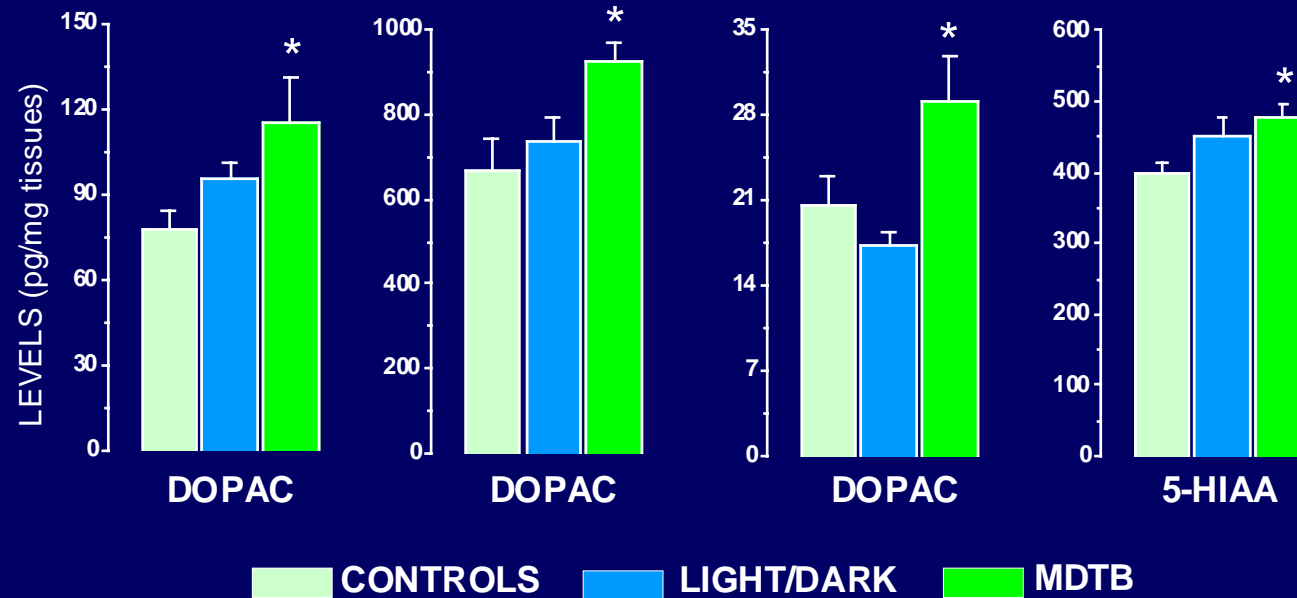
Effects of Exposure to the MDTB or to the Light/Dark Test on the Levels of Dopamine and 5-HT Metabolites in Various Brain Areas



FRONTAL CORTEX

STRIATUM

HIPPOCAMPUS



Main Factor Loadings of the Various Defensive Behaviors in the MDTB

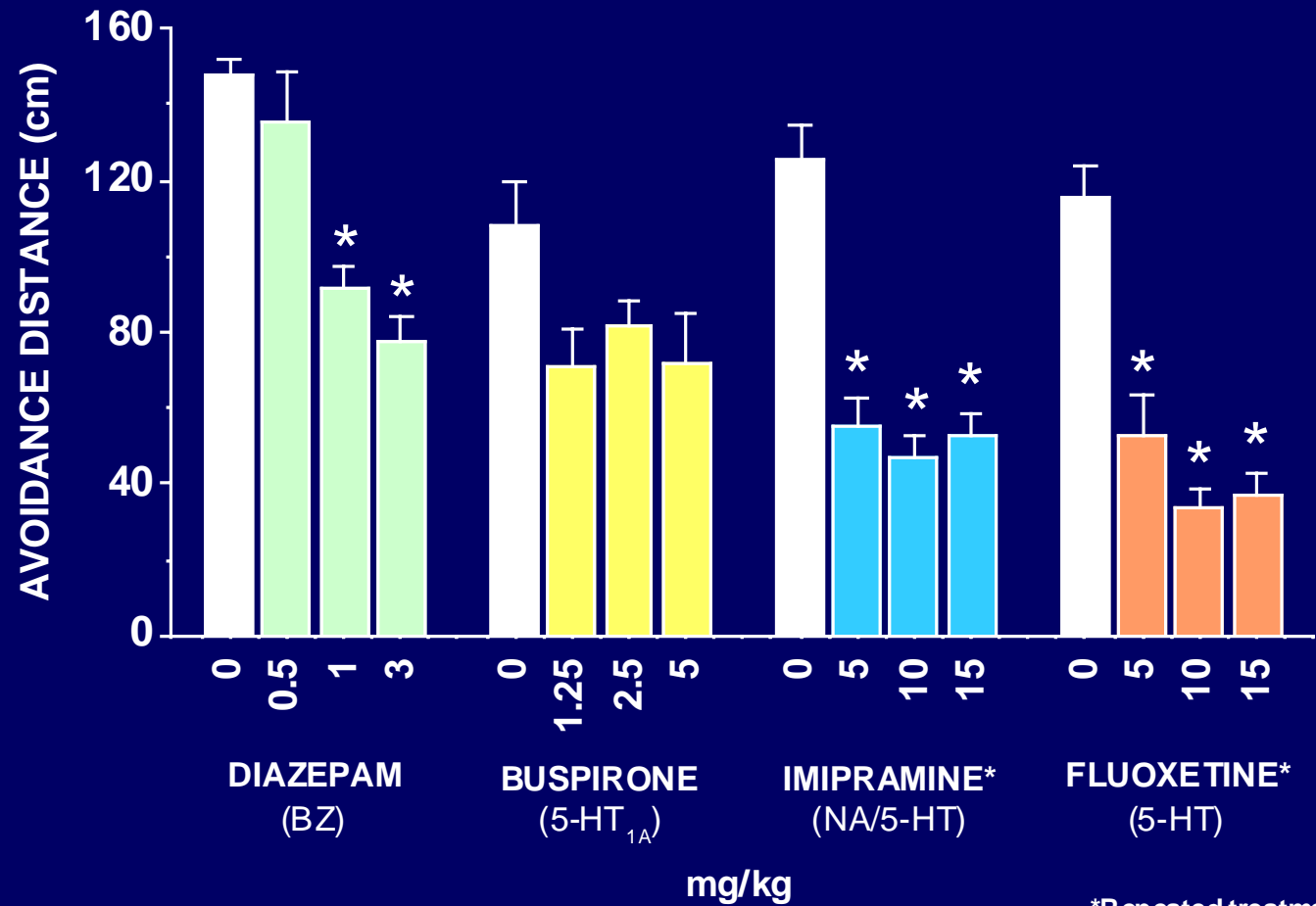
Factor 1	Factor 2	Factor 3	Factor 4
Risk Assessment	Flight	Defensive Aggression	Contextual Anxiety
<ul style="list-style-type: none"> • Stops • Orientations • Approaches followed by withdrawals 	<ul style="list-style-type: none"> • Avoidance distance • Avoidance frequency 	<ul style="list-style-type: none"> • Biting • Upright Posture 	<ul style="list-style-type: none"> • Escape attempts



Drugs Tested in the MDTB and Their Clinical Efficacy in the Management of Anxiety Disorders

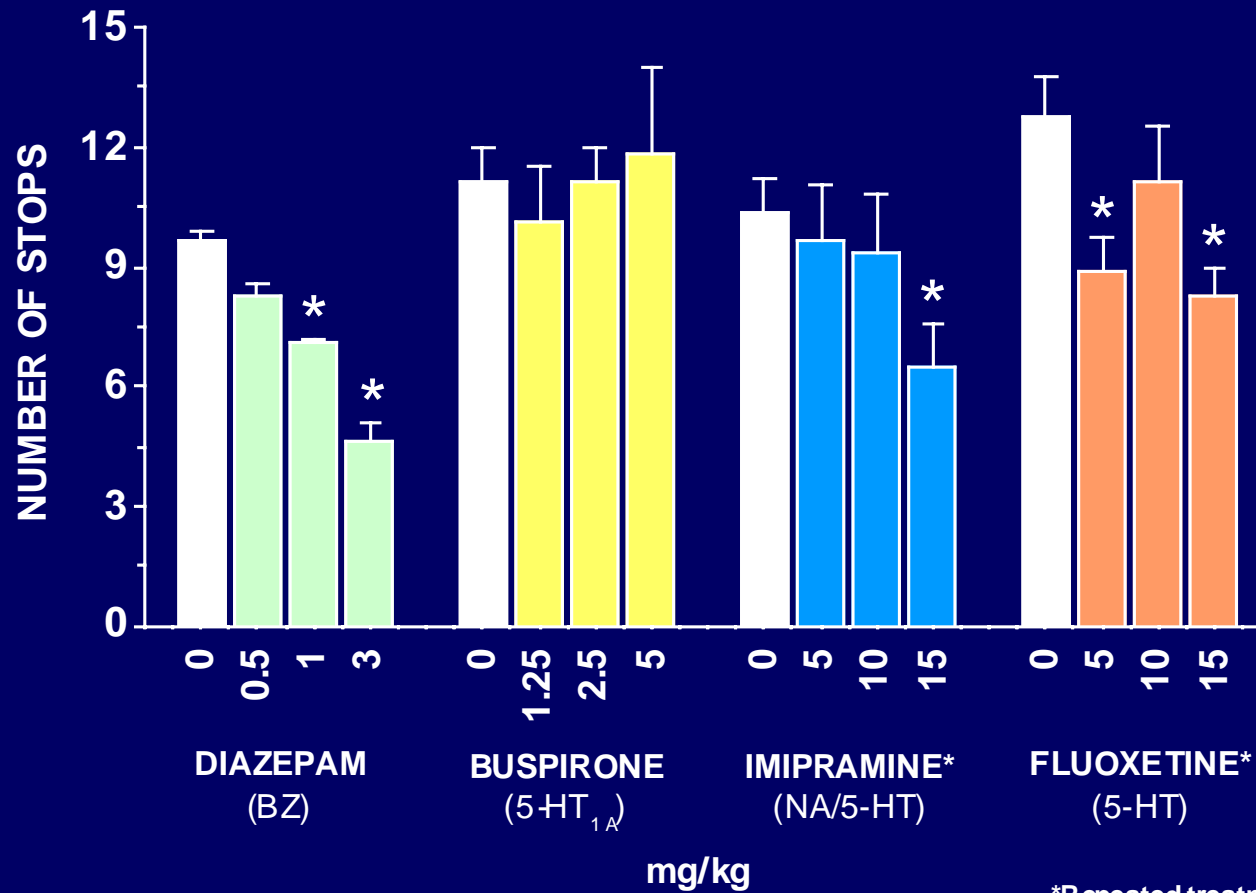
Drug	Action-Class	Generalized Anxiety Disorder	Panic Disorder
Alprazolam	BZ	+++	+++
Chlordiazepoxide	BZ	+++	
Clobazam	BZ	+++	++
Clonazepam	BZ	+++	+++
Clorazepate	BZ	+++	+
Diazepam	BZ	+++	++
Triazolam	BZ	+++	
Buspirone	5-HT _{1A} agonist	++	o
Imipramine	Tricyclic	++	+++
Fluoxetine	SSRI	+	++
Phenelzine	MAO _{AB} inhibitor	+	+++
Moclobemide	MAO _A inhibitor	o	+++

Effects of Several Reference Anxiolytic Agents on Flight Behavior in the MDTB



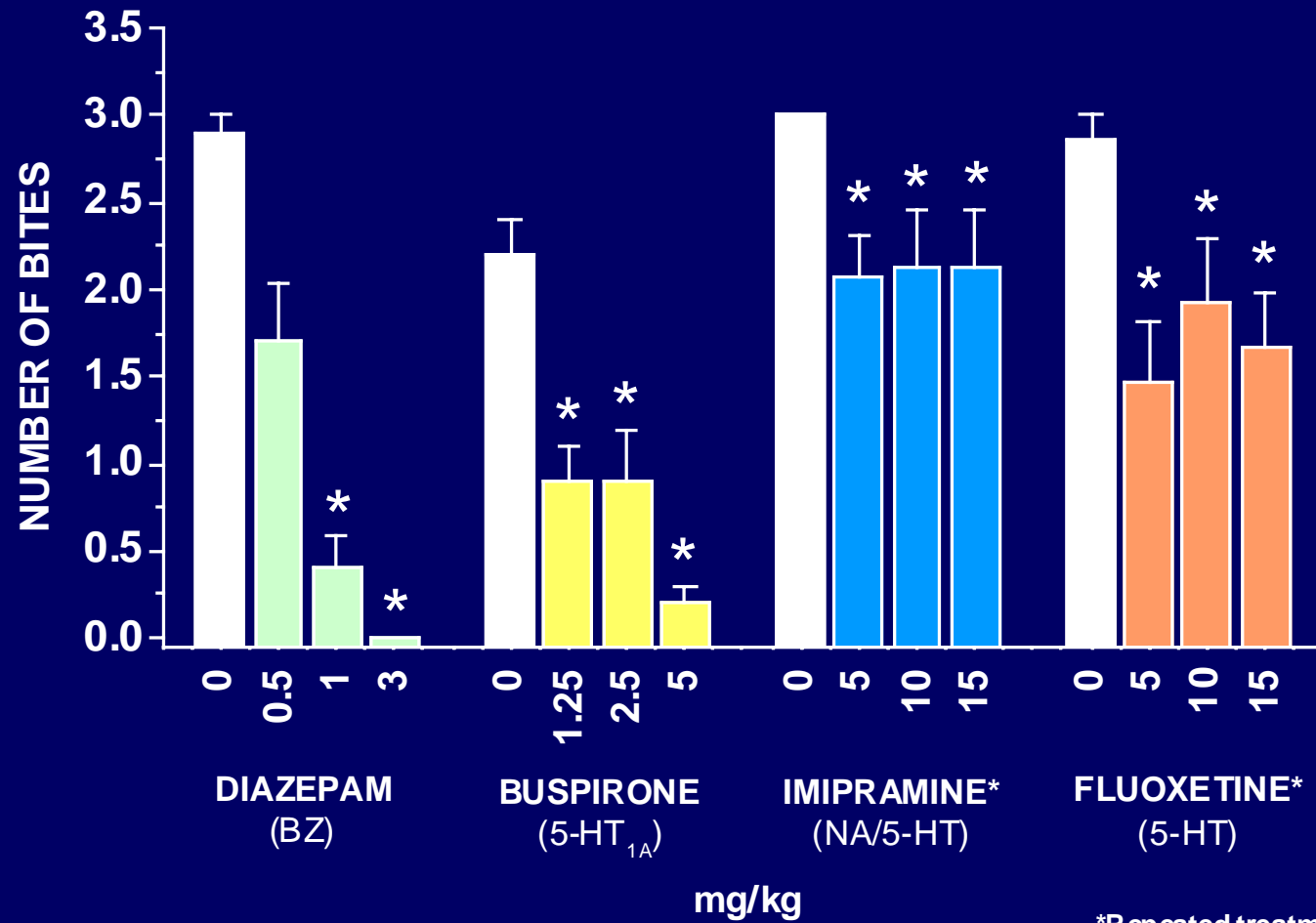
*Repeated treatment

Effects of Several Reference Anxiolytic Agents on Risk Assessment Behavior in the MDTB



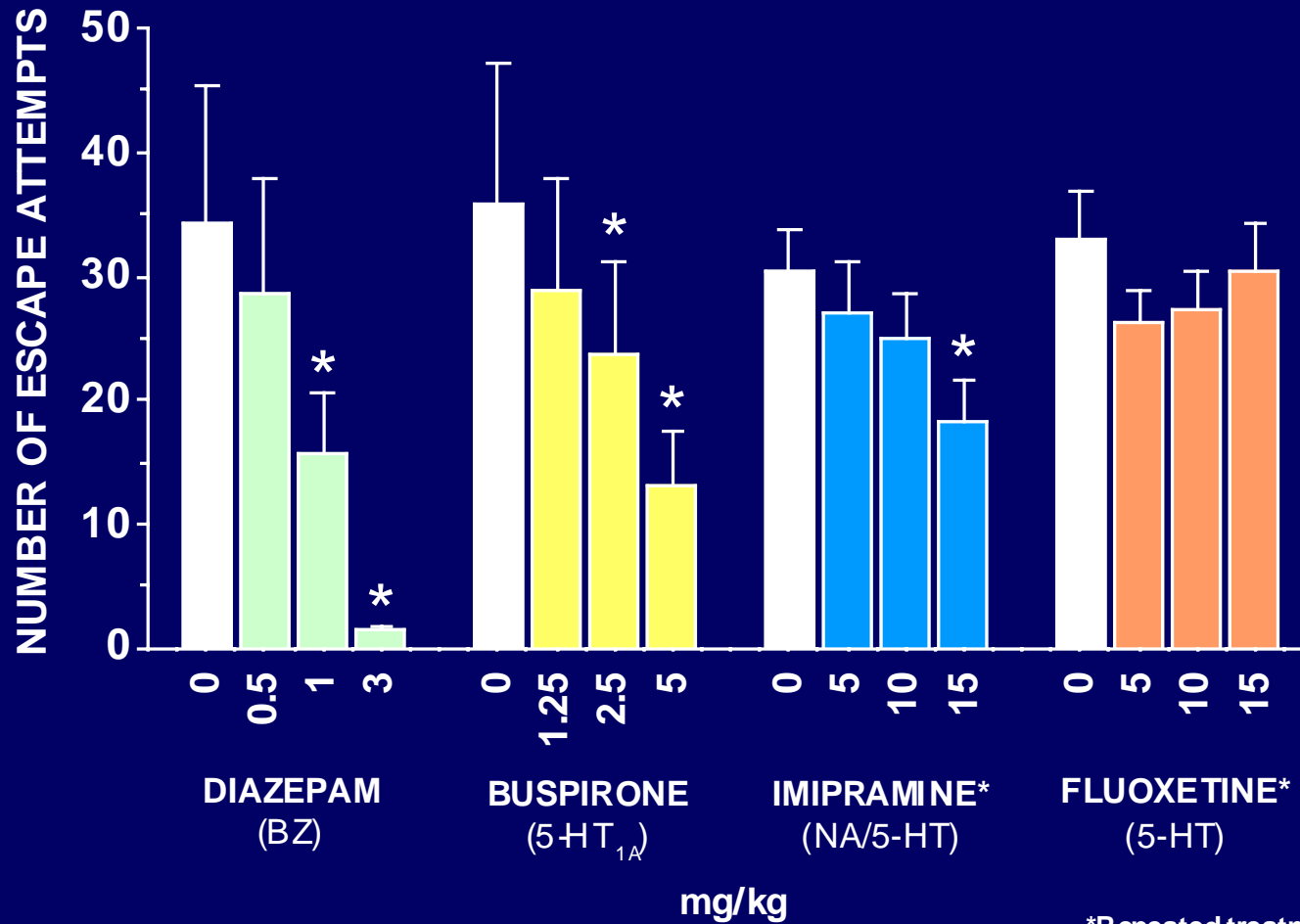
*Repeated treatment

Effects of Several Reference Anxiolytic Agents on Defensive Aggression in the MDTB



*Repeated treatment

Effects of Several Reference Anxiolytic Agents on Contextual Anxiety in the MDTB



*Repeated treatment

Summary of the Effects of Various Anxiolytic Agents on Defensive Behavior in the MDTB

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	+
Moclobemide	MAO _A inhibitor	++	o	o	o

(+) at sedative doses

MDTB

**FACTOR 1
"Risk Assessment"**

**FACTOR 2
"Flight"**

**FACTOR 3
"Defensive
Aggression"**

**FACTOR 4
"Contextual
Anxiety"**

**Generalized
Anxiety Disorder**

Panic Disorder

**Generalized
Anxiety Disorder**

**Anticipatory
Anxiety**

**(Cognitive
Aspects)**

**(Affective
Aspects)**

Main Neuropeptides Studied in Models of Anxiety

- ◆ CHOLECYSTOKININ (CCK)
- ◆ CORTICOTROPIN-RELEASING FACTOR (CRF)
- ◆ NEUROPEPTIDE Y (NPY)
- ◆ NEUROTENSIN
- ◆ ORPHANIN FQ (OFQ)
- ◆ TACHYKININS (SP, NKA, NKB)

CCK and Anxiety

- ◆ Discovered in 1928. There are multiple active forms of CCK (eg. CCK_{8s}, CCK₄)
- ◆ CCK_B receptors are widely distributed in the CNS, with high levels found in the cortex, olfactory bulb, nucleus accumbens, amygdala, hippocampus and hypothalamus
- ◆ Administration of CCK agonists (eg. pentagastrin, CCK_{8s}) produces behavioral changes indicative of fear in animals and in human

CRF and Anxiety

- ◆ 41-residue peptide originally isolated from ovine hypothalamus in 1981
- ◆ CRF is the major hypophysiotropic factor regulating basal and stress-induced release of ACTH
- ◆ Effects of CRF are mediated by two receptors (CRF₁ and CRF₂), both located in brain structures known to be involved in the modulation of anxiety (eg. limbic system, hypothalamic areas)
- ◆ Central infusion of CRF produces behavioral effects similar to those observed when animals are exposed to stress
- ◆ CRF levels are increased in post-traumatic stress disorder

Neurokinin-A and Anxiety

- ◆ Belongs to the tachykinins, a group of neuropeptides, including SP and NK-B
- ◆ NK-A is the preferred endogenous peptide for the NK₂ receptor, which is present in discrete regions of CNS (eg. septum, hippocampus, thalamus)
- ◆ Central infusion of NK-A produces anxiogenic-like effects in rodents

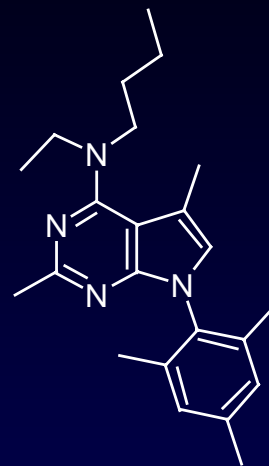
Neurotensin and Stress

- ◆ 13-amino-acid discovered in 1971
- ◆ In the brain (10 %), highest concentrations of NT in the hypothalamus, substantia nigra, periaqueductal gray matter, limbic system (eg. nucleus accumbens, septum and amygdala)
- ◆ Two subtypes of NT receptor have been described, NT-1R and NT-2R
- ◆ Central and systemic injections of NT stimulate ACTH secretion in rats

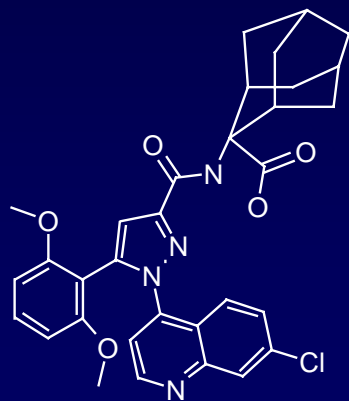
Examples of Neuropeptide Receptor Antagonists Tested in the MDTB



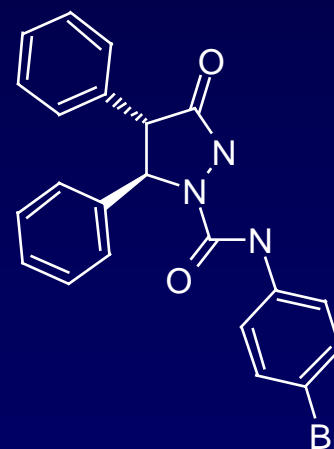
SR48968
(NK₂)



CP-154,526
(CRF₁)

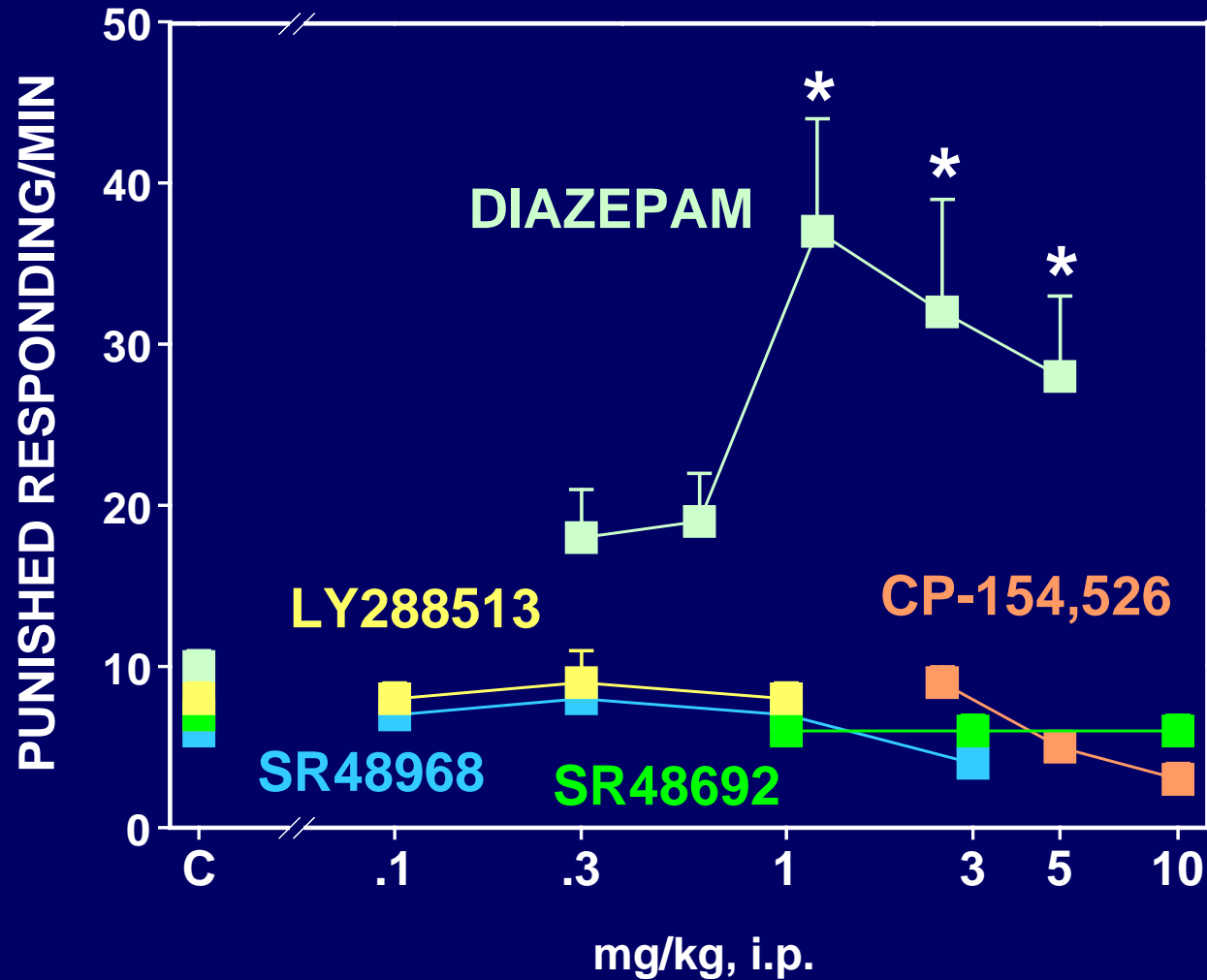


SR48692
(NT₁)

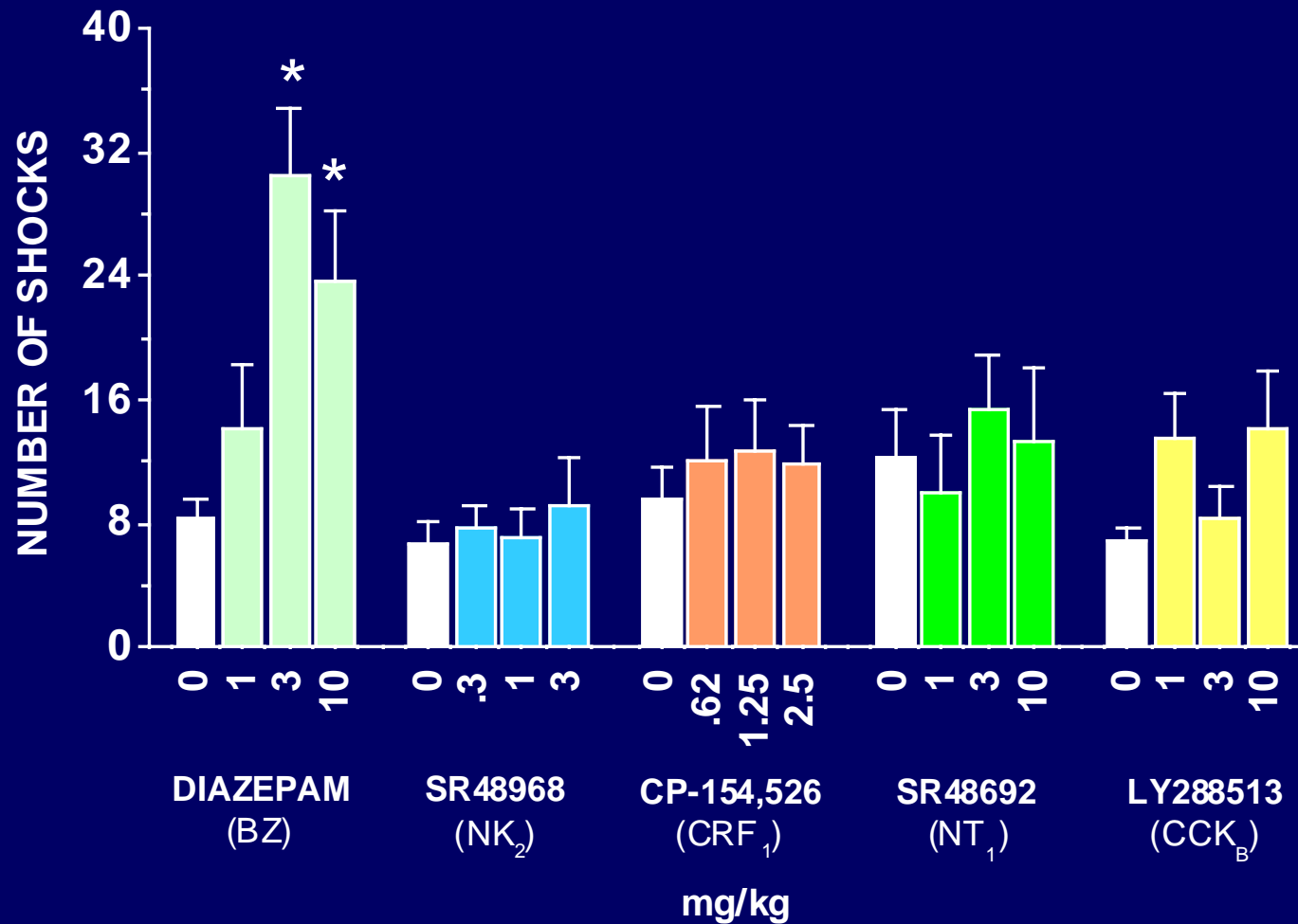


LY288513
(CCK_B)

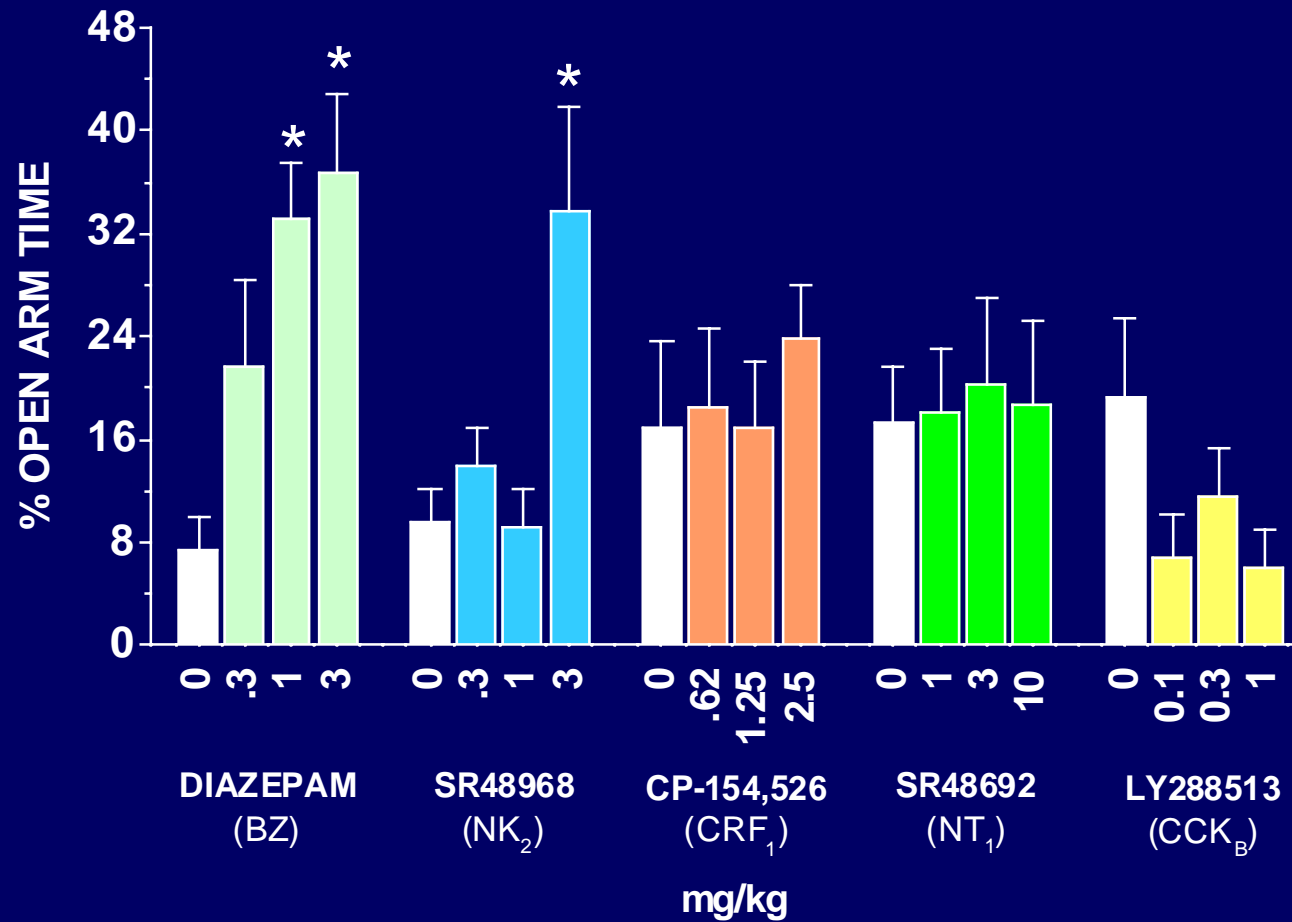
Effects of Various Neuropeptide Receptor Antagonists in the Lever Pressing Conflict Test in Rats



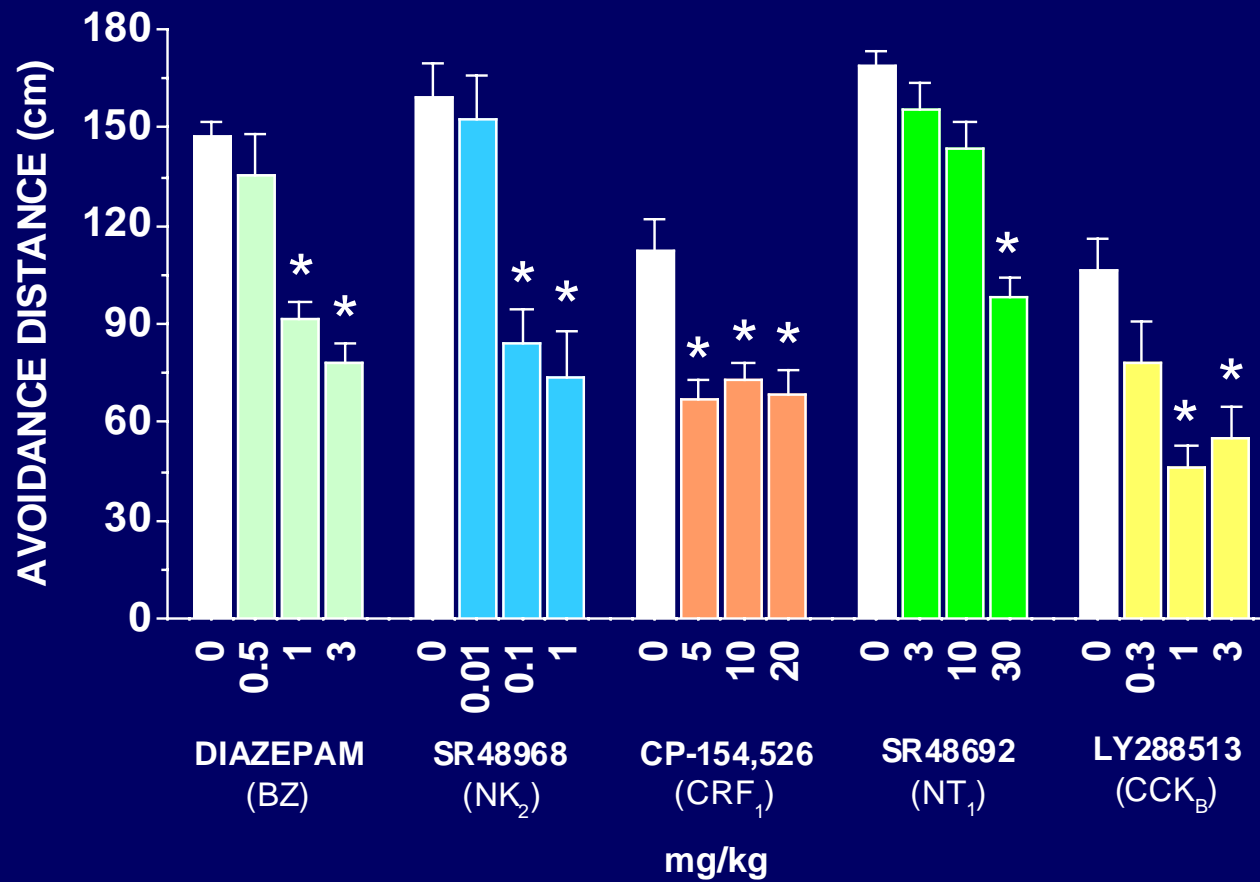
Effects of various Neuropeptide Receptor Antagonists in the Punished Drinking Conflict Test in Rats



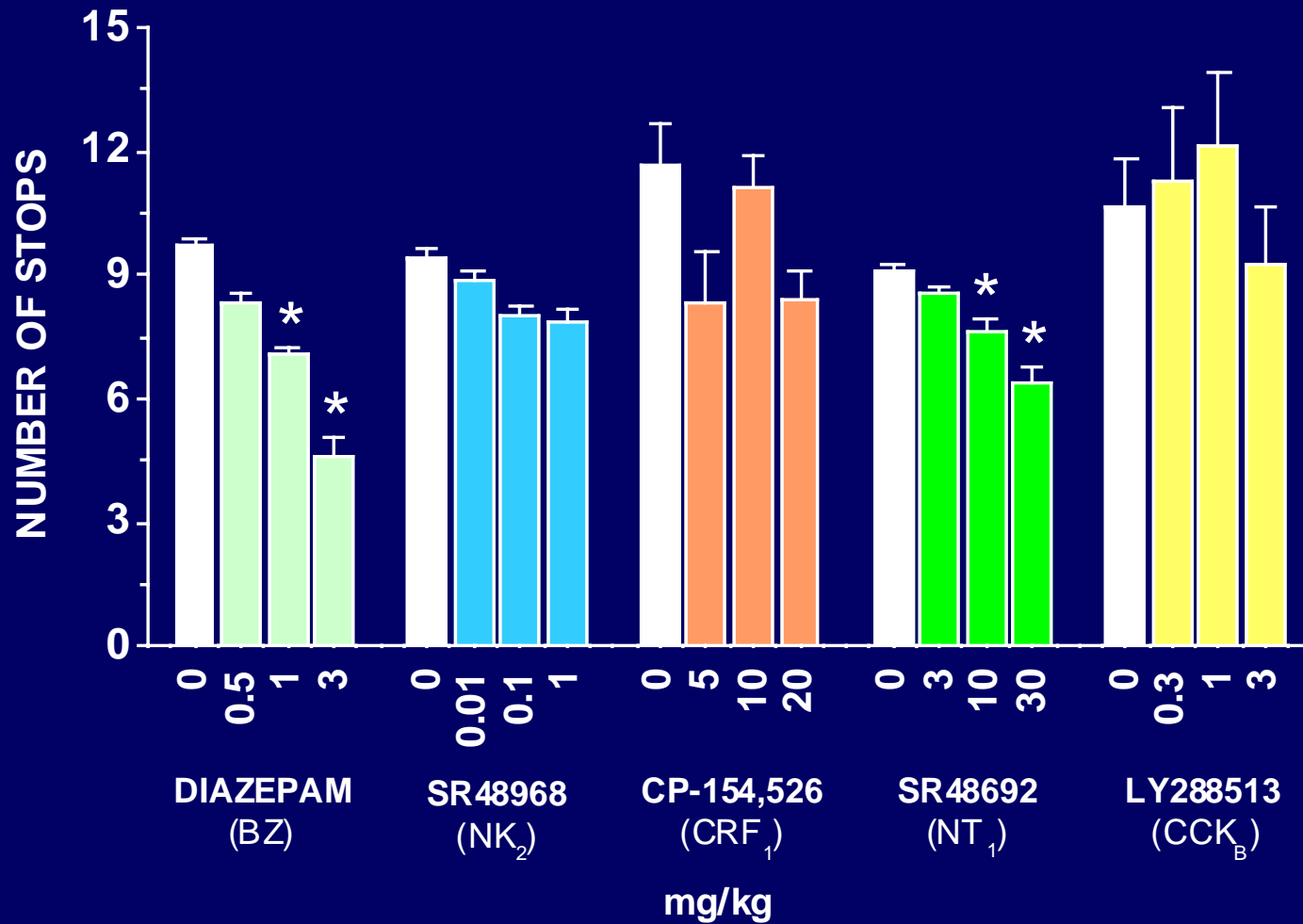
Effects of various Neuropeptide Receptor Antagonists in the Elevated Plus-Maze Test in Rats



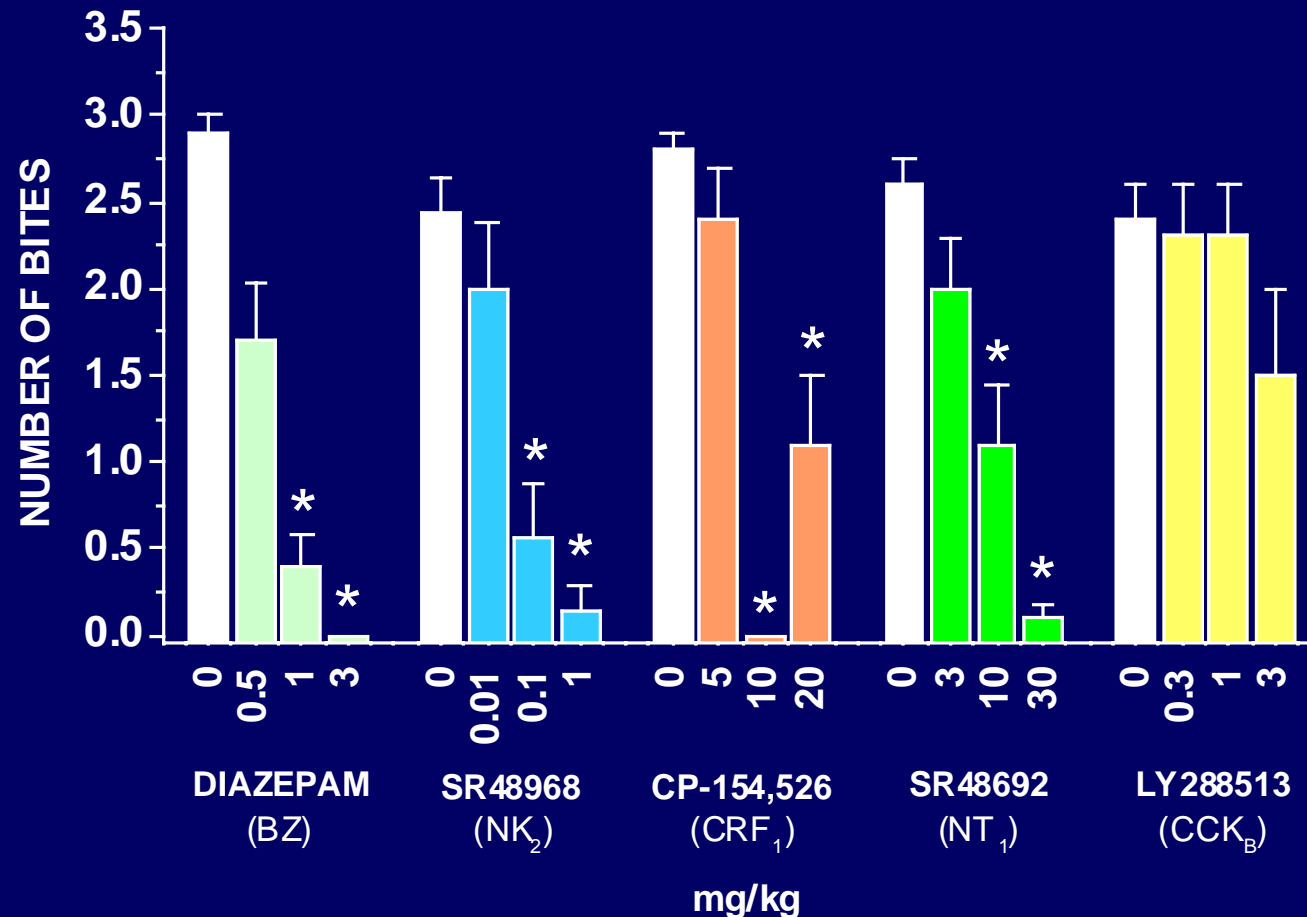
Effects of various Neuropeptide Receptor Antagonists on Flight Behavior in the MDTB



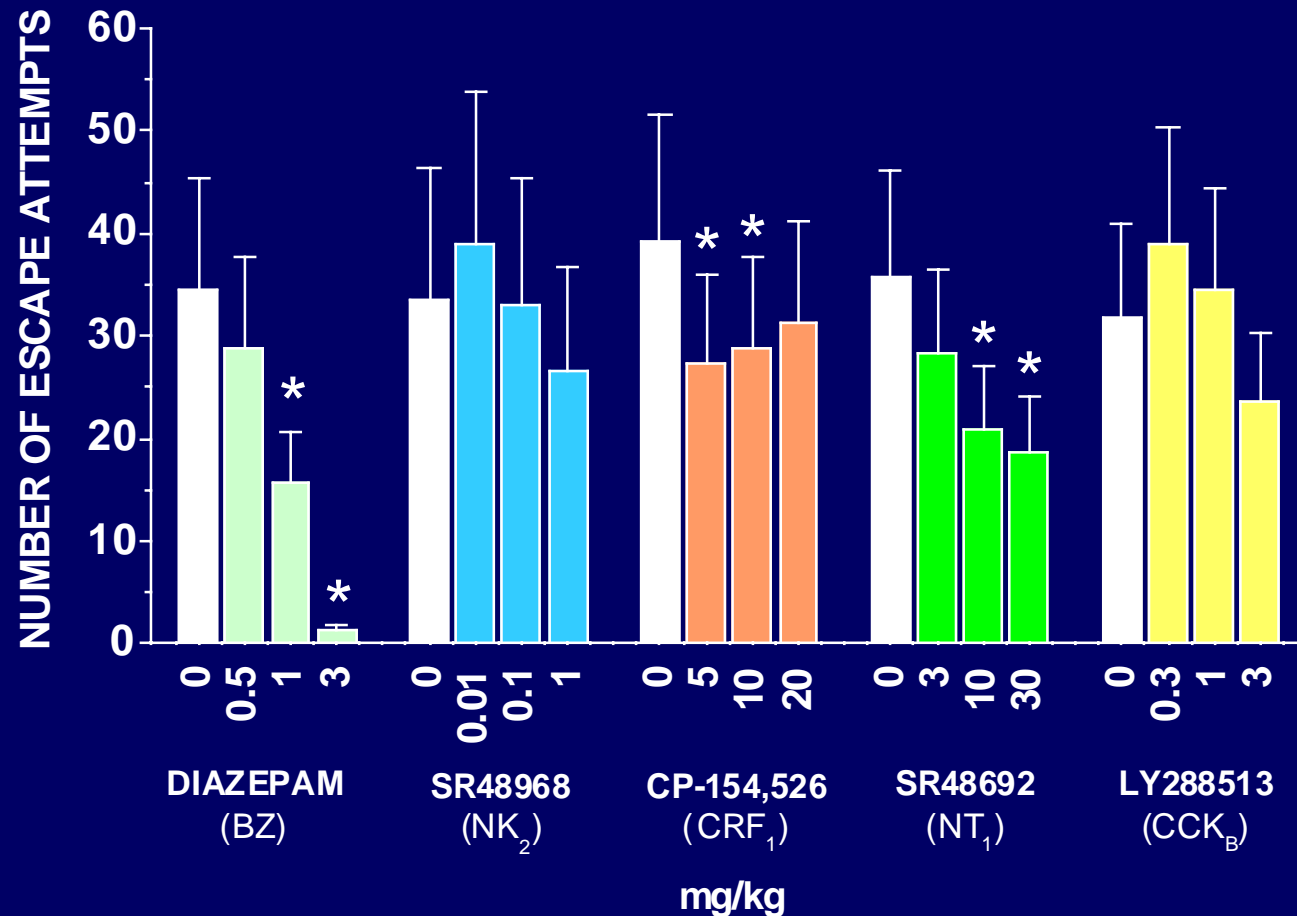
Effects of various Neuropeptide Receptor Antagonists on Risk Assessment Behavior in the MDTB



Effects of various Neuropeptide Receptor Antagonists on Defensive Aggression in the MDTB



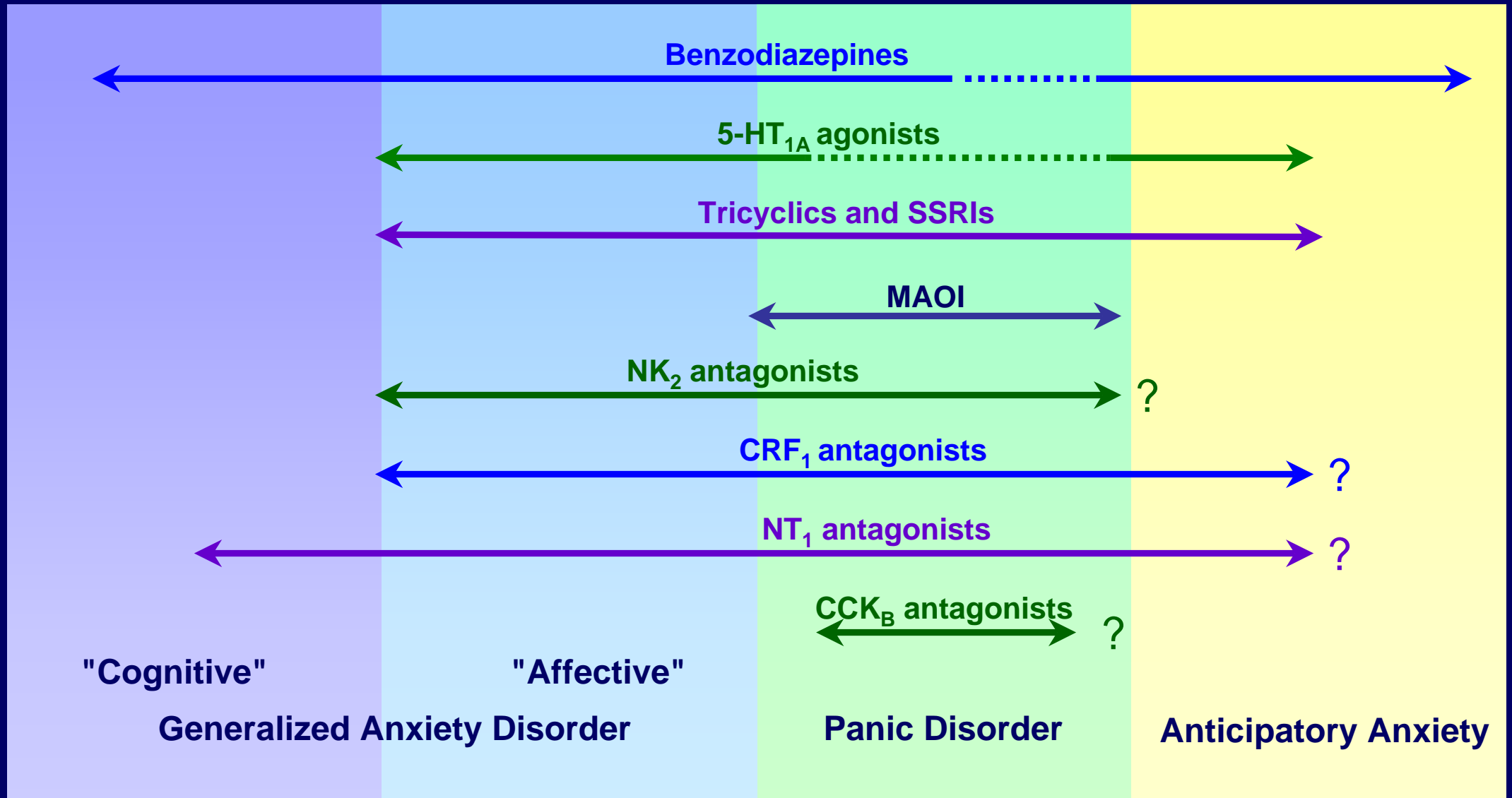
Effects of various Neuropeptide Receptor Antagonists on Contextual Anxiety in the MDTB



Summary of the Effects of Various Neuropeptide Receptor Antagonists on Defensive Behavior in MDTB

	Action-Class	Flight	Risk Assessment	Defensive Aggression	Contextual Anxiety
Diazepam	BZ	++	++	+++	+++
SR48968	NK ₂ antagonist	++	o	+++	o
CP-154,526	CRF ₁ antagonist	++	o	+	+
SR48692	NT ₁ antagonist	+	+	++	++
LY288513	CCK _B antagonist	+	o	o	o

Known or Expected Clinical Spectrum of Therapeutic Activity of Various Clinically Effective and Potential Anxiolytics



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- Blanchard R.
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