

RATIONALE FOR DEVELOPMENT OF
NK₂ ANTAGONISTS AS ANXIOLYTICS
AND ANTIDEPRESSANTS

1990

?

2000

« No apparent
expression of SKR
(NK₂) mRNA in the
CNS »

(Eur. J. Biochem 193 : 751 -57)

First clinical trial
(Phase IIa) with a
selective NK₂
antagonist in major
depressive disorder

Tissue distribution and quantitation of the mRNAs for three rat tachykinin receptors

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salivary glands and small and large intestines. In contrast, NKR mRNA is predominantly expressed in the nervous system, particularly in the cortex, hypothalamus and cerebellum, whereas SKR mRNA expression is restricted to the peripheral tissues, being abundant in the urinary bladder, large intestine, stomach and adrenal gland. Thus, the mRNAs for the three tachykinin receptors show distinct patterns of expression between the nervous system



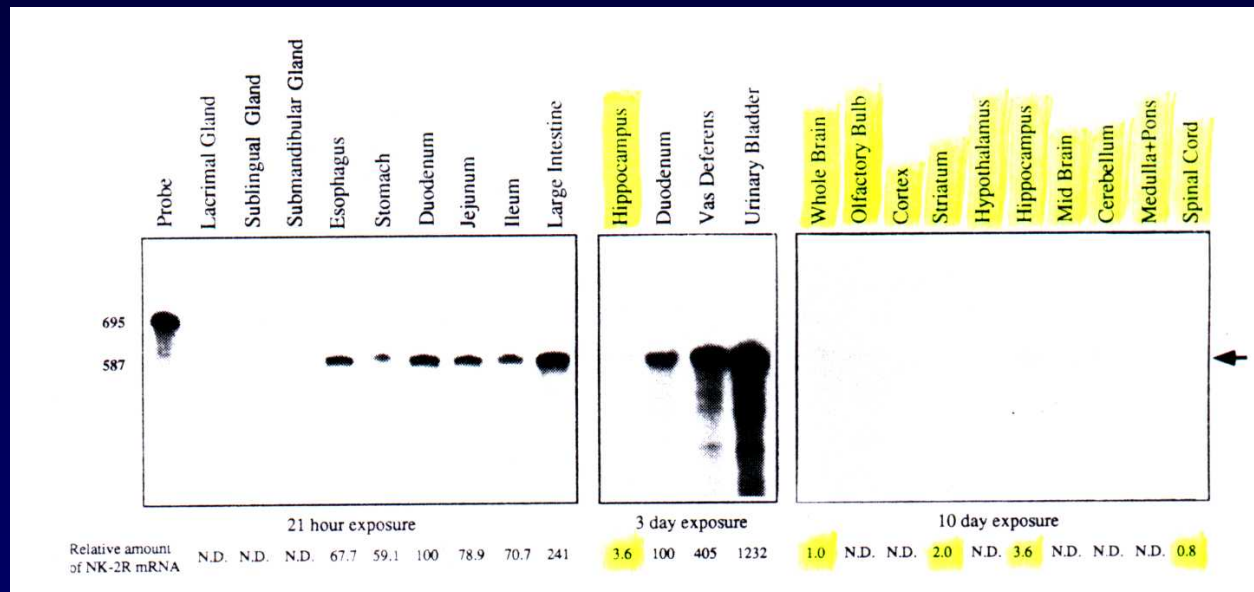
Regions or tissues	Relative mRNA level for		
	SPR	NKR	SKR
Whole brain	1.0	1.2	n.d.
Cortex	0.7	1.4	n.d.
Hypothalamus	2.1	1.6	n.d.
Midbrain	0.8	0.3	n.d.
Striatum	1.1	0.1	n.d.
Hippocampus	0.4	0.3	n.d.
Olfactory bulb	1.8	1.0	n.d.
Cerebellum	0.05	1.6	n.d.
Medulla/pons	0.9	0.3	n.d.
Spinal cord	1.1	0.5	n.d.
Stomach	0.4	0.2	3.1
Duodenum	0.8	0.02	0.9
Small intestine	2.0	0.06	0.8
Large intestine	3.5	0.1	4.3
Eye	0.9	1.9	0.5
Parotid gland	1.7	n.d.	n.d.
Submandibular and sublingual glands	4.2	<0.01	n.d.
Heart	n.d.	<0.01	n.d.
Lung	0.2	n.d.	n.d.
Liver	n.d.	<0.01	n.d.
Adrenal gland	n.d.	<0.01	3.6
Kidney	n.d.	0.06	n.d.
Spleen	0.3	n.d.	n.d.
Urinary bladder	5.3	0.4	6.6
Testis	n.d.	n.d.	0.2
Skin	0.4	n.d.	n.d.

Eur. J. Biochem. 193 : 751-57, 1990

Pharmacological and Molecular Biological Studies on the Diversity of Rat Tachykinin NK-2 Receptor Subtypes in Rat CNS, Duodenum, Vas Deferens, and Urinary Bladder^a

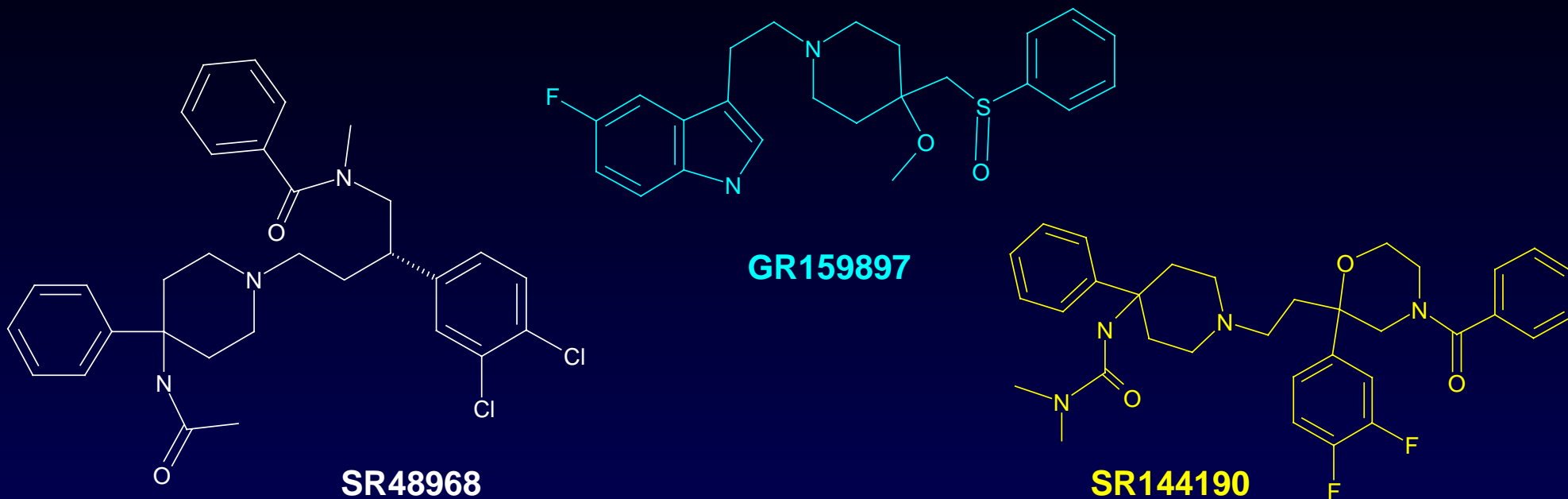
YASUO TAKEDA AND JAMES E. KRAUSE

*Department of Anatomy and Neurobiology
Washington University School of Medicine
St. Louis, Missouri 63110*



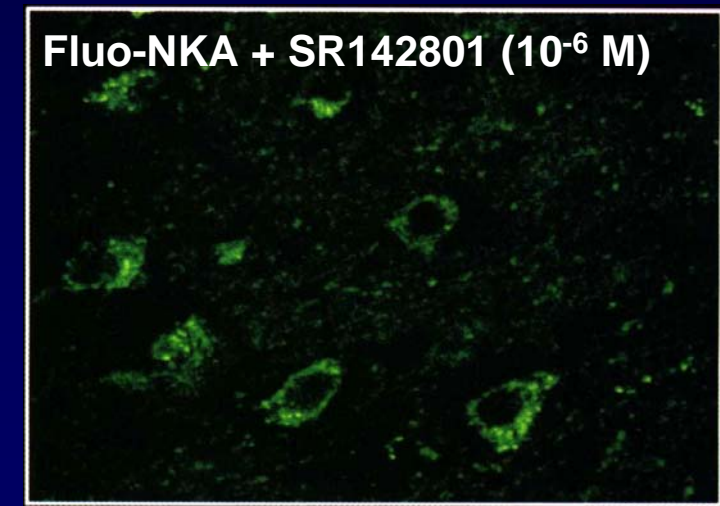
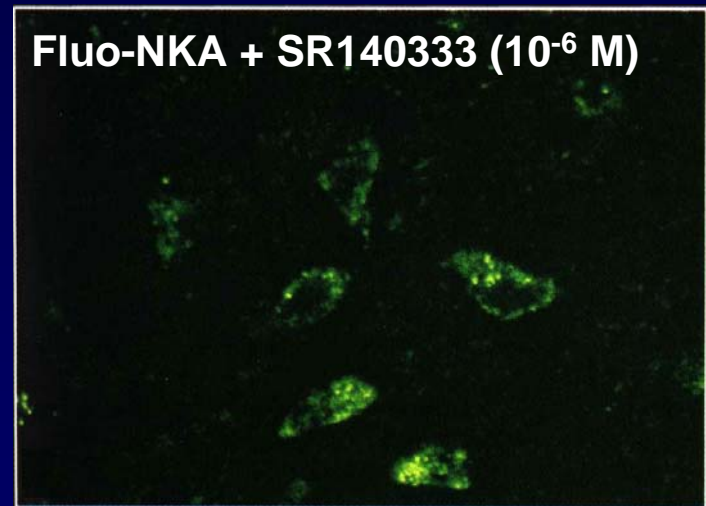
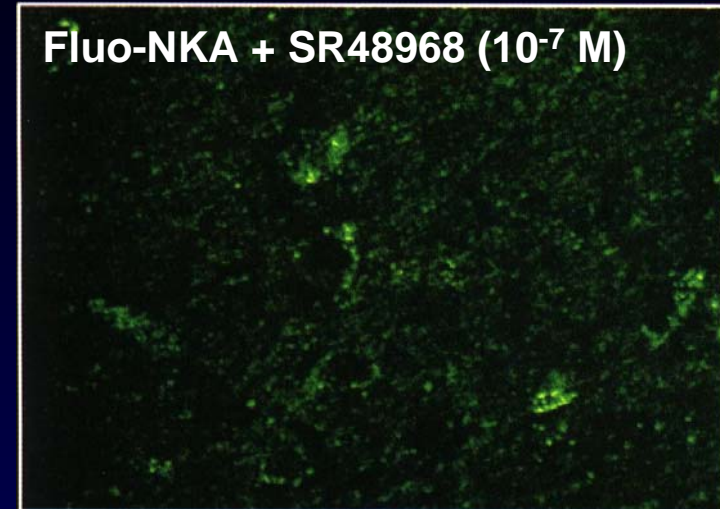
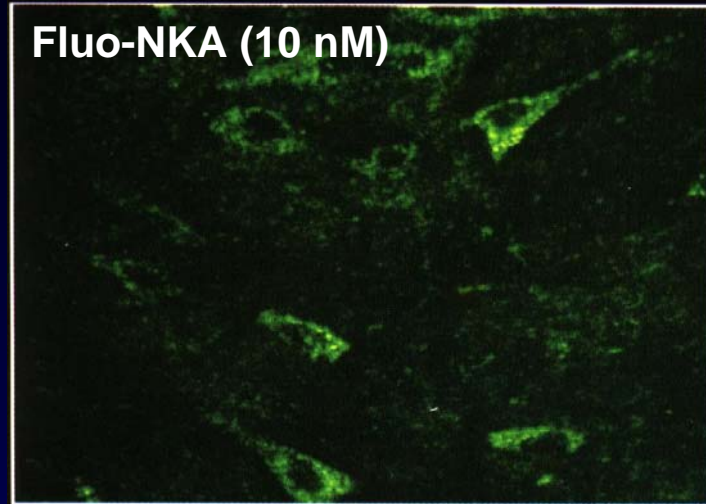
Ann. N.Y. Acad. Sci. 632 : 479-82, 1991

Selective and potent non-peptide NK₂ receptor antagonists

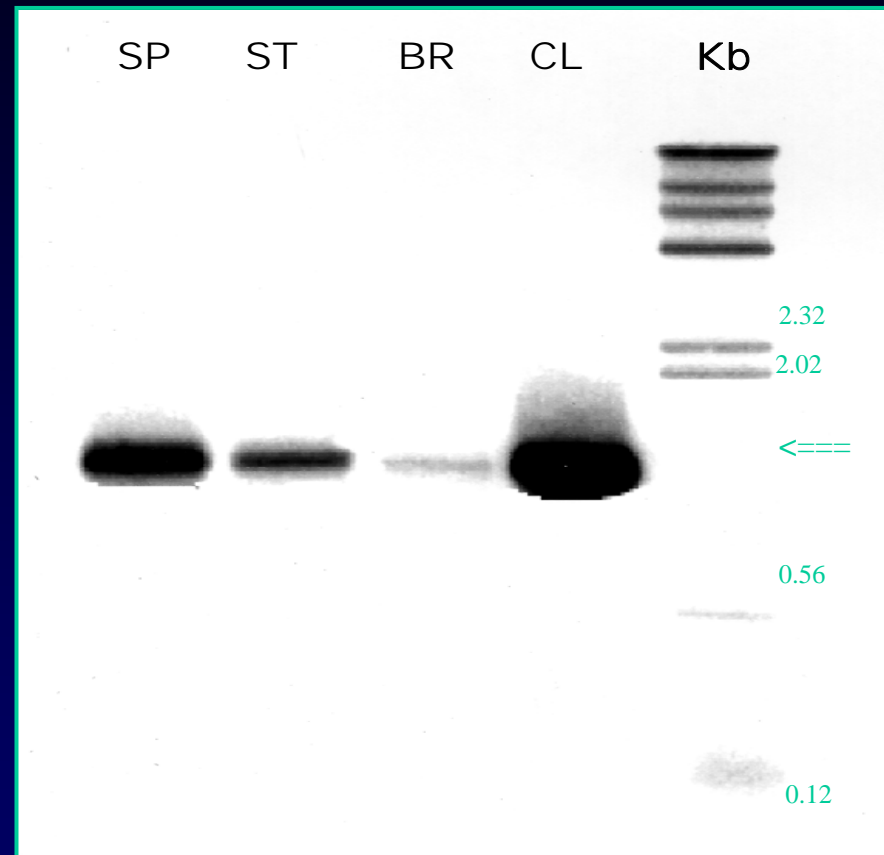


	hNK ₂ -CHOpKi	pA ₂	
GR159897	9.5	8.72	Beresford et al. (1995)
SR48968	9.9	10.3	Emonds-Alt et al. (1992)
SR144190		10.1	Emonds-Alt et al. (1997)

Evidence of the presence of NK₂ binding sites in the septal area of rats using a fluorescent-tagged neurokinin A (NKA) derivative

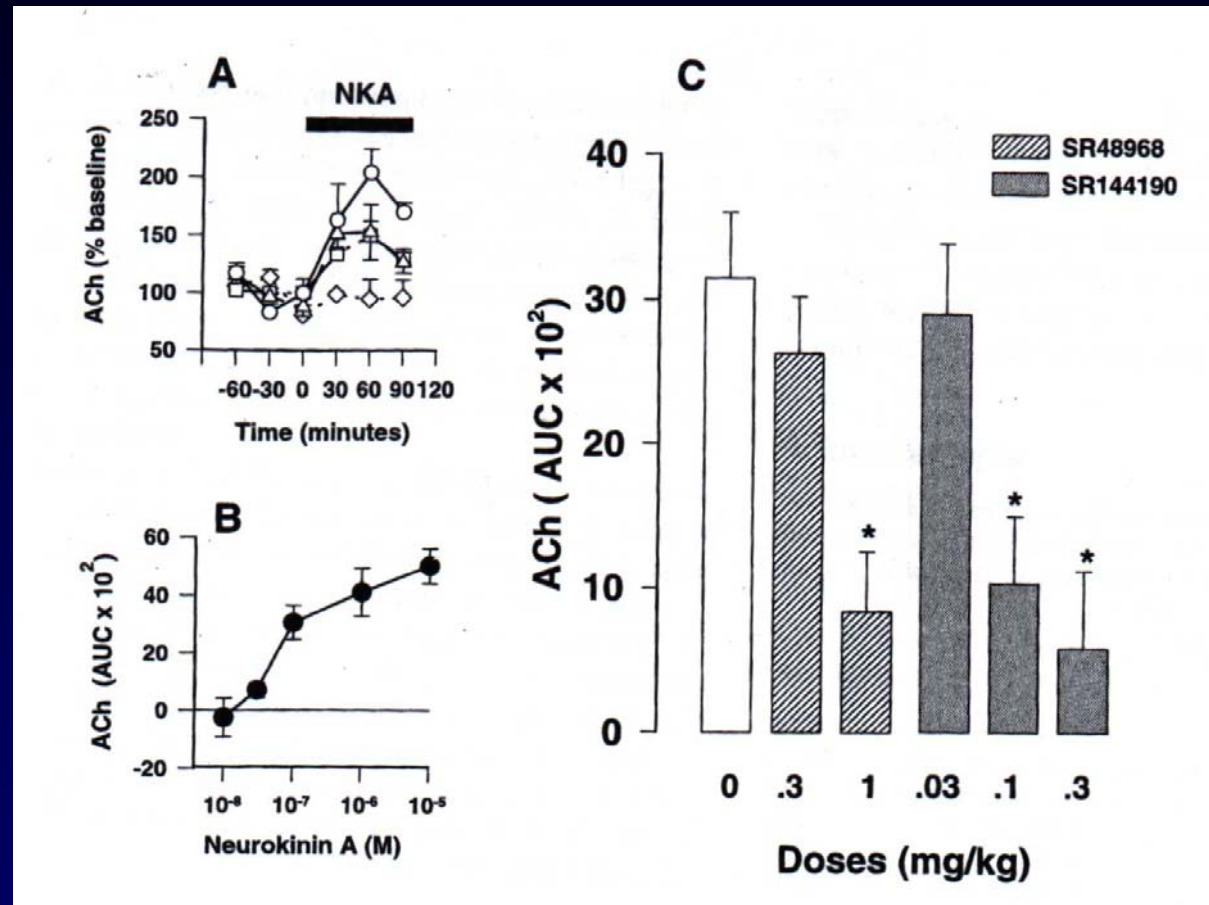


Analysis by RT-PCR of NK₂ receptor expression in various rat tissues including septum (SP), striatum (ST), whole brain (BR) and colon (CL)



Steinberg et al., *Eur. J. Neurosci.* 10 : 2337-45, 1998

Effects of septal application of NKA on extracellular hippocampal ACh release



Steinberg et al. *Eur. J. Neurosci.* 10 : 2337-45, 1998

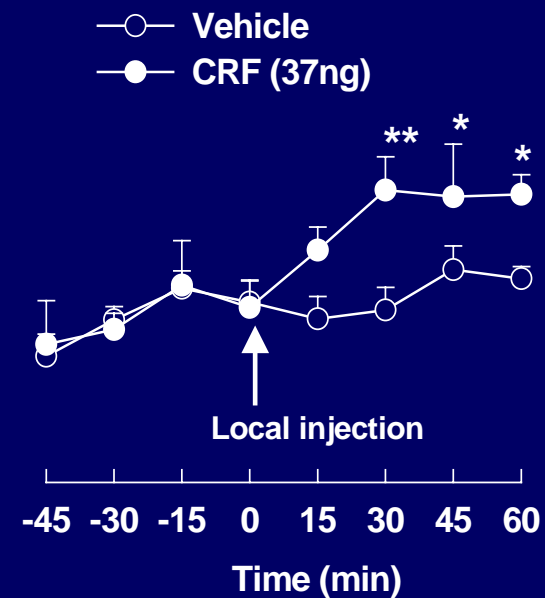
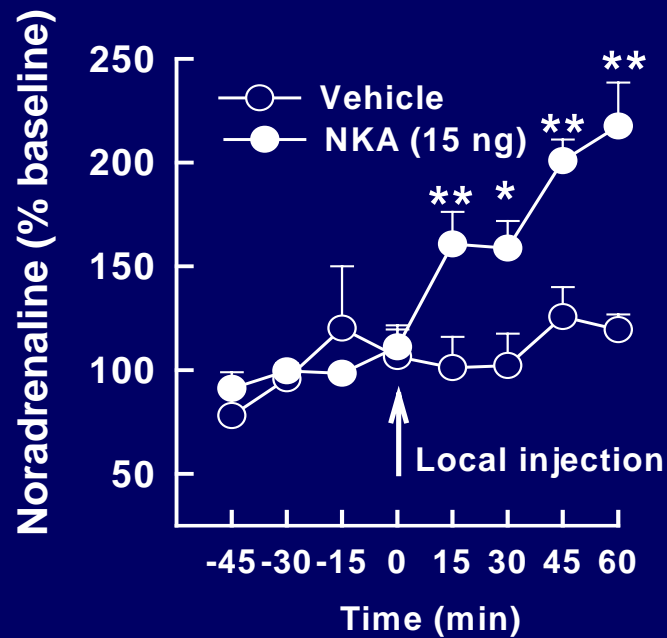
Structure and properties of rat tachykinin receptors

	NK ₁	NK₂	NK ₃
Amino acid residues	407	452	390
Molecular weight	46.364	51.104	43.851
Preferred endogenous peptide	Substance P	Neurokinin A	Neurokinin B
Core homology	66 % to NKA 54 % to NKB	55 % to NKB	
2nd messenger	IP ₃ -Ca ²⁺	IP₃-Ca²⁺	IP ₃ -Ca ²⁺
Expression Sites			
Nervous system	+++	+	+++
Peripheral tissues	+++	++	+++

Does central infusion of the preferred
NK₂ endogenous peptide NKA
modulate stress response?

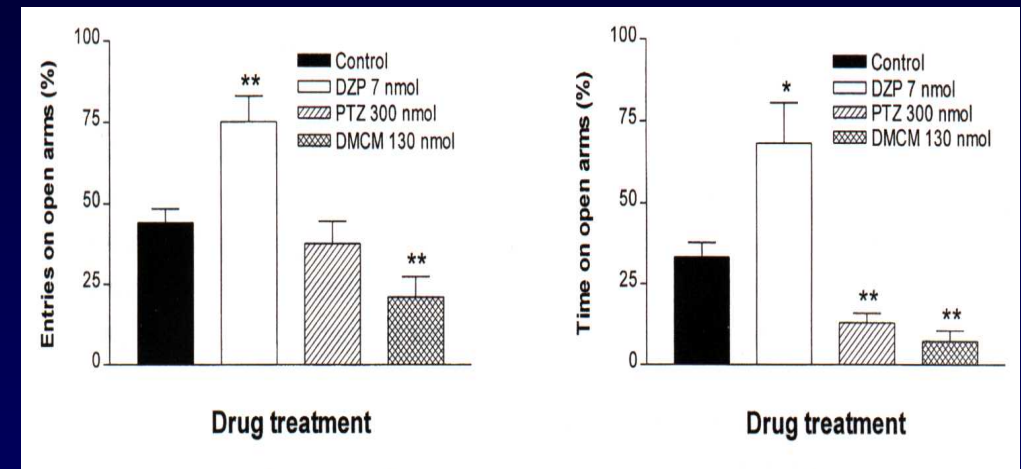
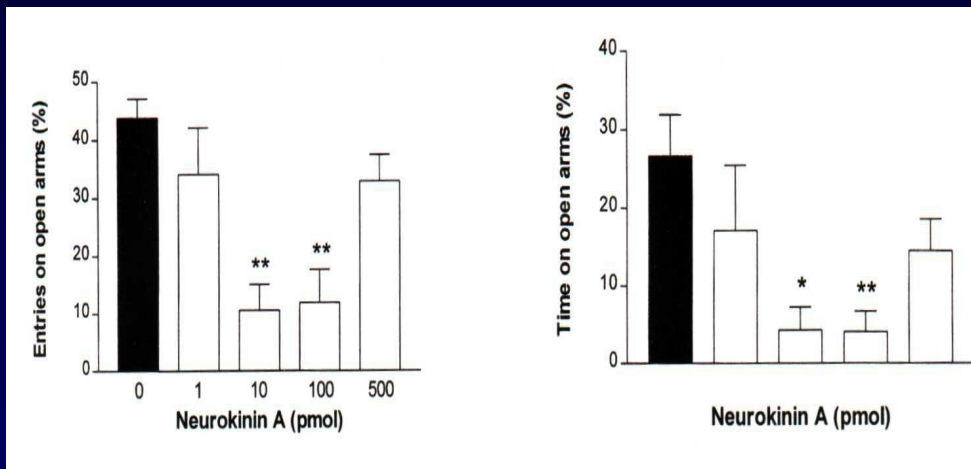
Evidence from neurochemical and
behavioral studies

Effects of neurokinin A and CRF microinfused into the locus coeruleus on prefrontal cortex NE release



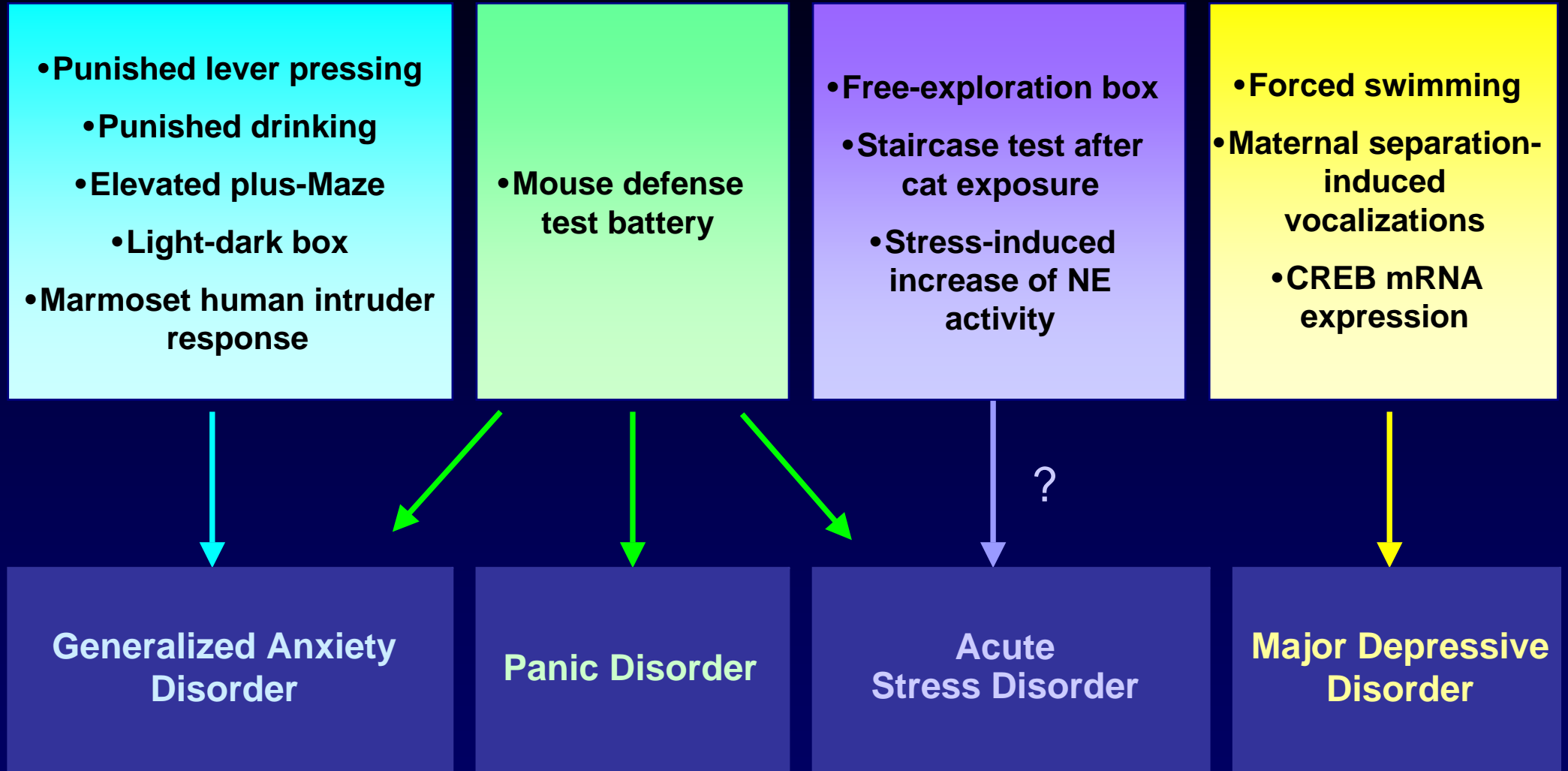
Steinberg et al.

Effects of central administration of NKA in the elevated plus-maze test in mice : comparison with benzodiazepine receptor ligands



Do selective NK₂ receptor
antagonists modulate emotional
behaviors ?

Animal models used to investigate the effects of NK₂ receptor antagonists on emotional processes

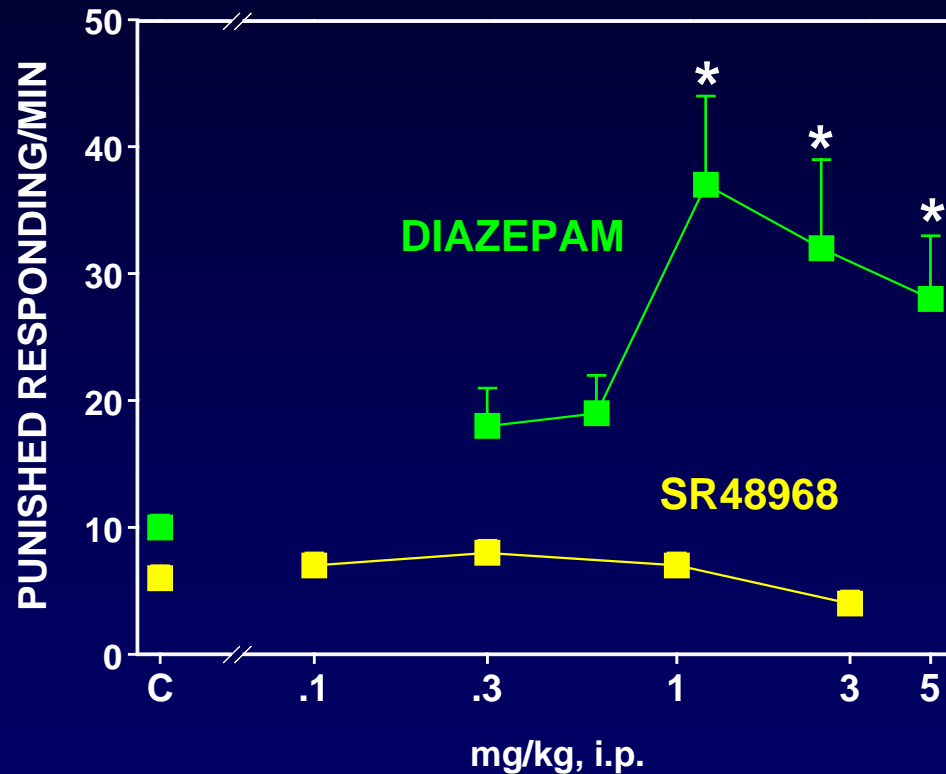


Do NK₂ receptor antagonists have
anxiolytic-like properties ?

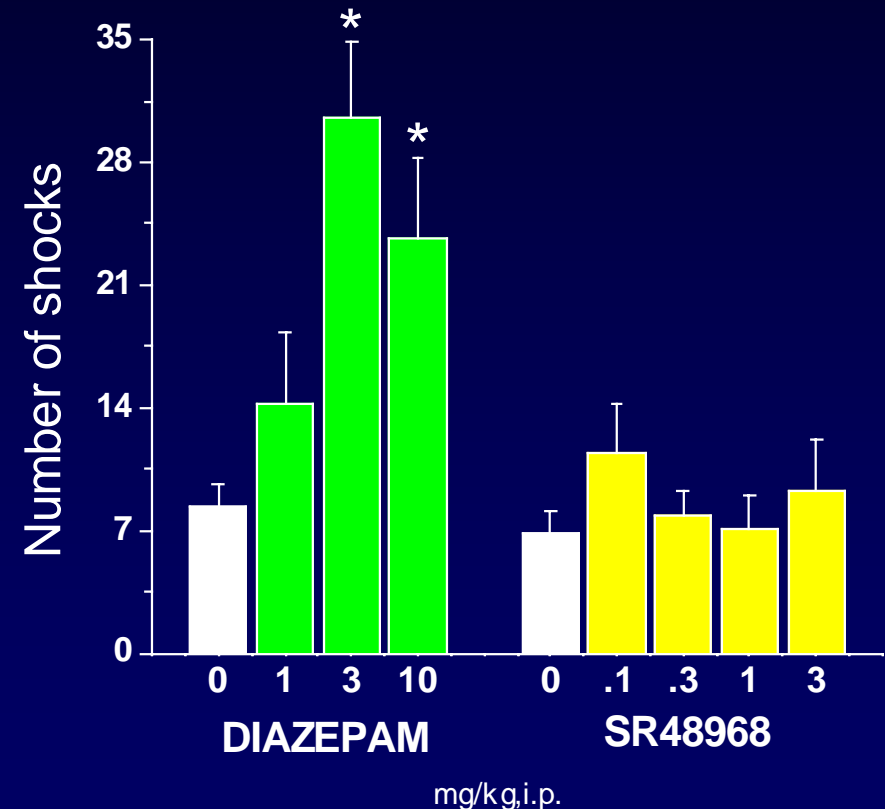
Evidence from behavioral and
neurochemical models of
anxiety/stress disorders

Effects of a selective NK₂ receptor antagonist in two traditional conflict models in rats

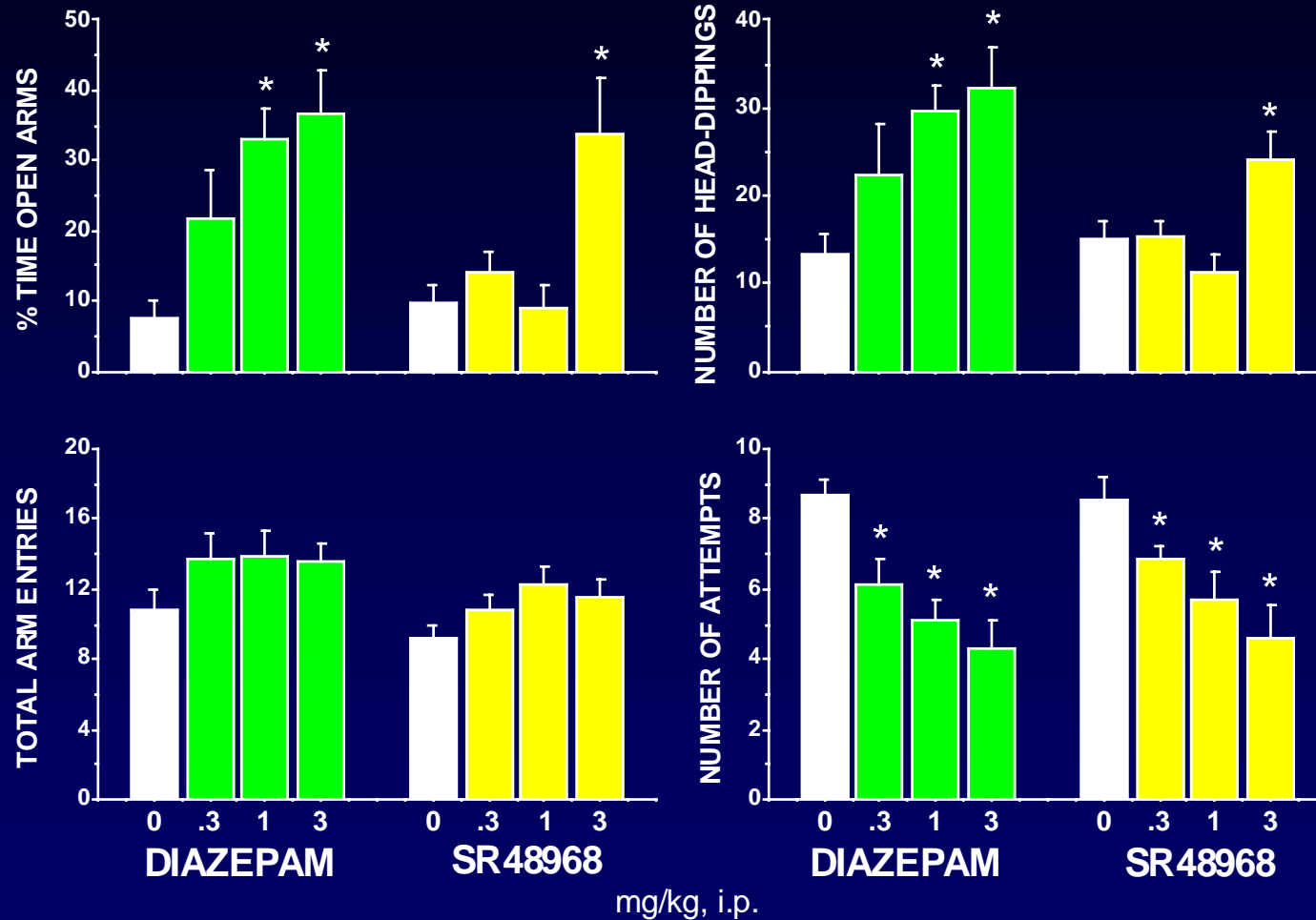
Punished lever pressing test



Punished drinking test



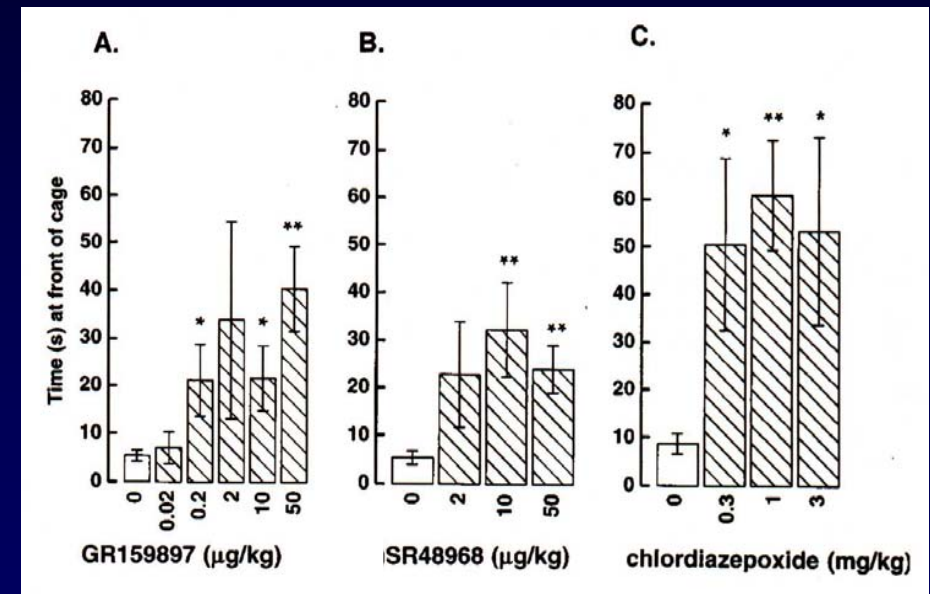
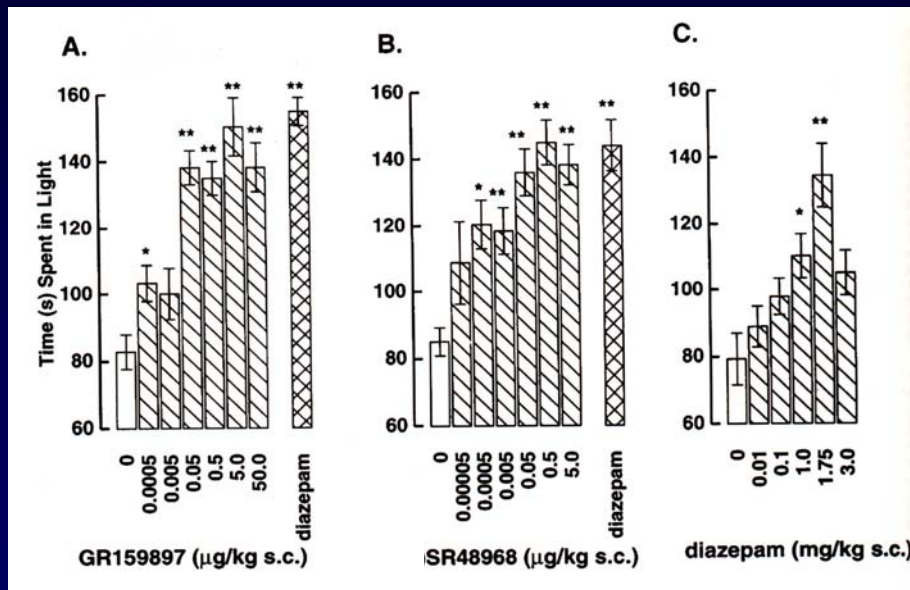
Effects of a selective NK₂ receptor antagonist in the elevated plus-maze test in rats



Effects of selective NK₂ receptor antagonists in animal models of anxiety

Mouse light-dark box

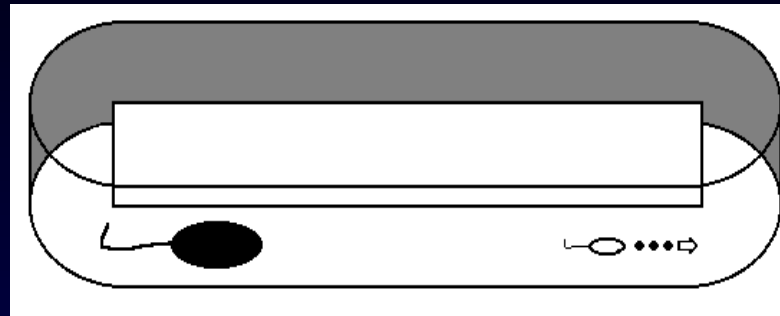
Marmoset human intruder response test



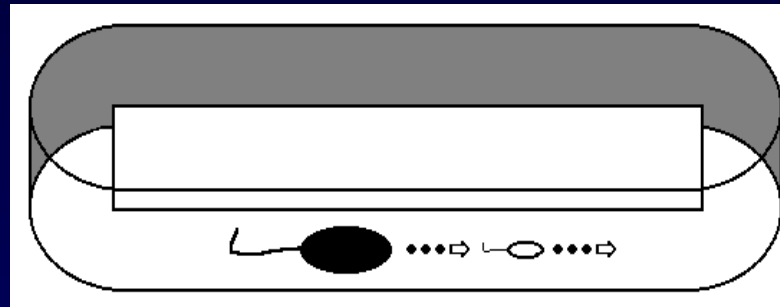
Walsh et al., *Psychopharmacology* 121 : 186-91, 1995

The mouse defense test battery

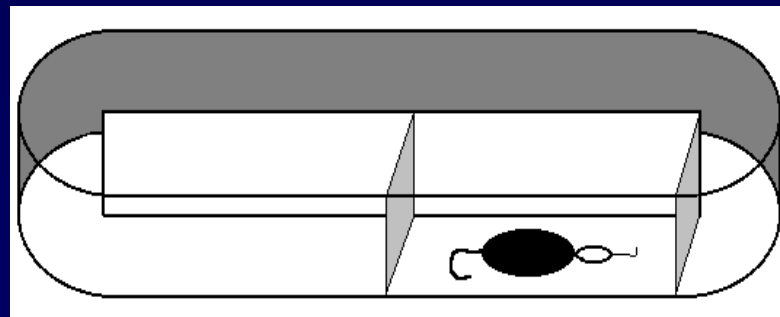
FLIGHT



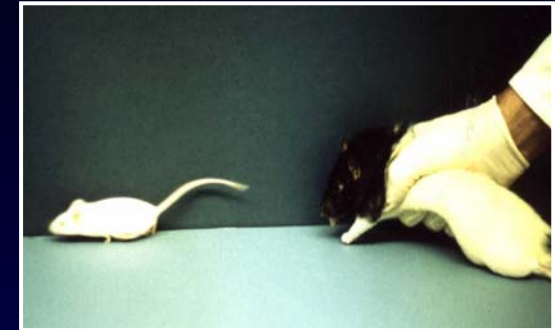
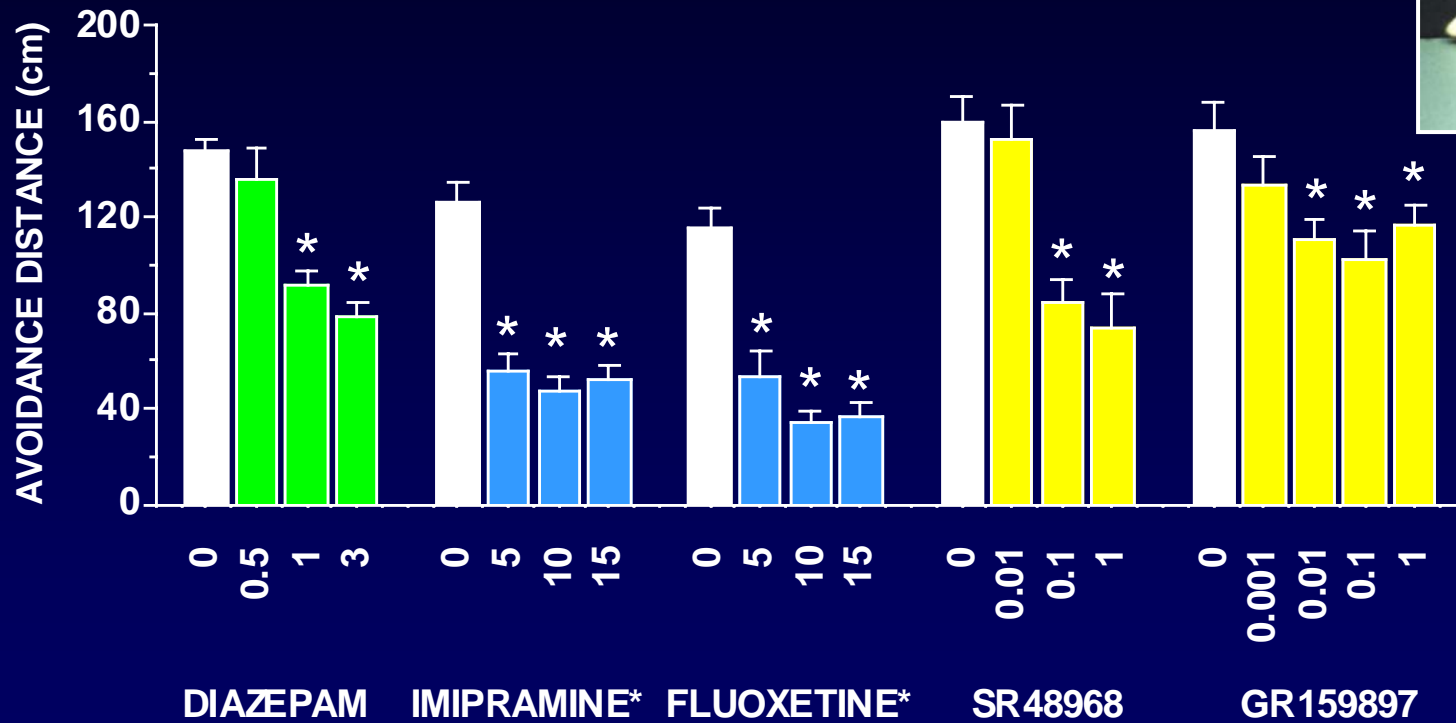
**RISK
ASSESSMENT**



**DEFENSIVE
AGGRESSION**



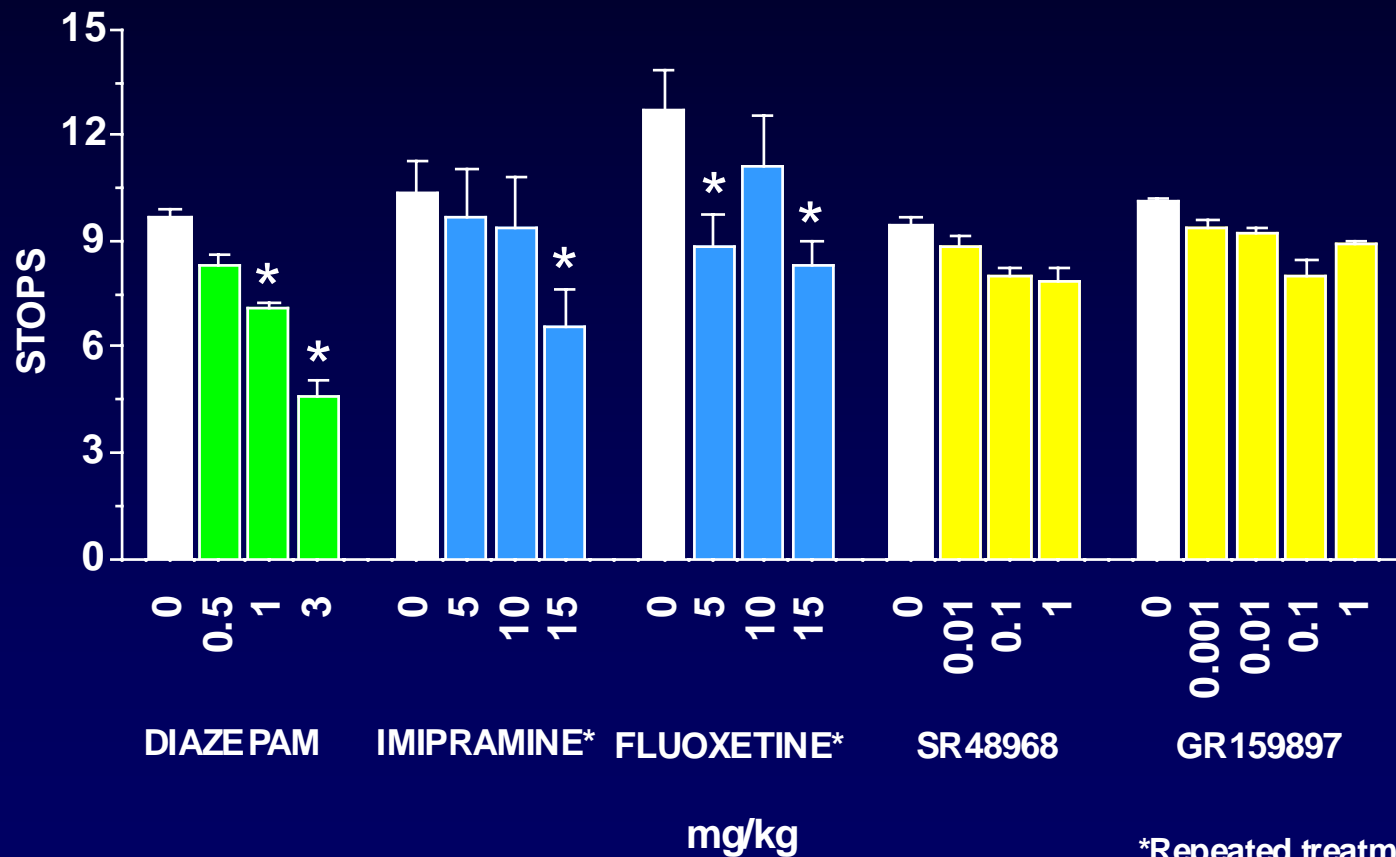
Effects of selective NK₂ receptor antagonists on flight behavior in the mouse defense test battery



mg/kg

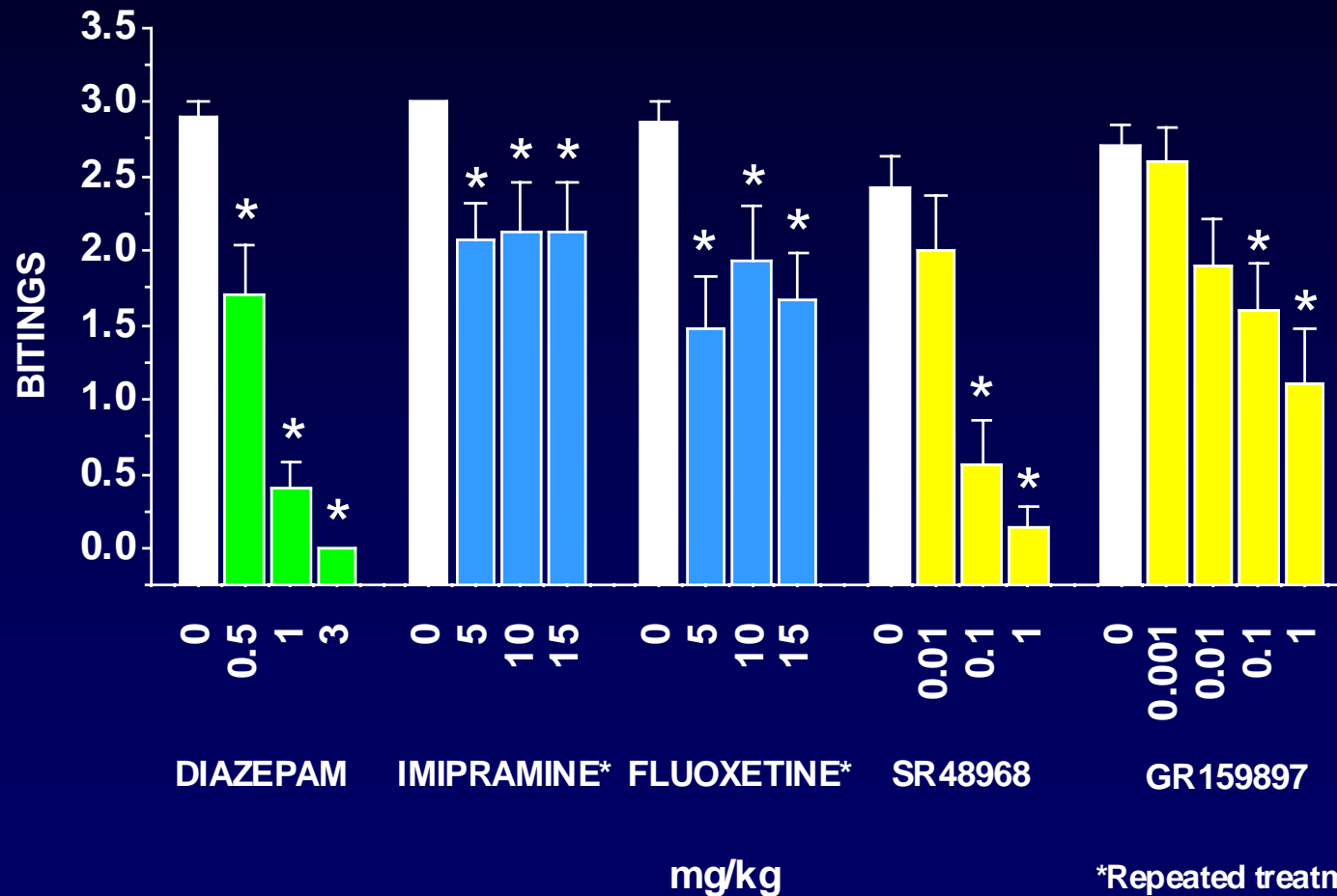
*Repeated treatment

Effects of selective NK₂ receptor antagonists on risk assessment behavior in the mouse defense test battery



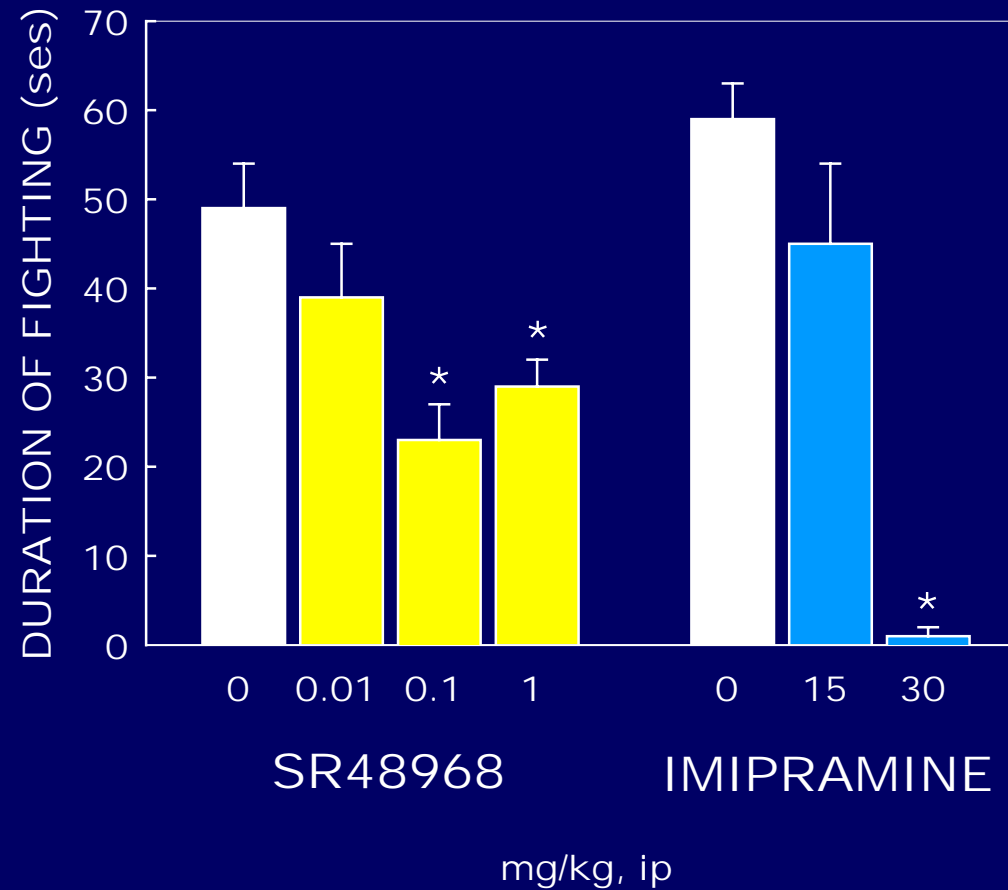
*Repeated treatment

Effects of selective NK₂ receptor antagonists on defensive aggression in the mouse defense test battery



*Repeated treatment

Effects of a selective NK₂ receptor antagonist on isolation-induced aggression in mice



Investigation of
the behavior of
rodents
following cat
exposure



Cat exposure (5-10 min)

60 min

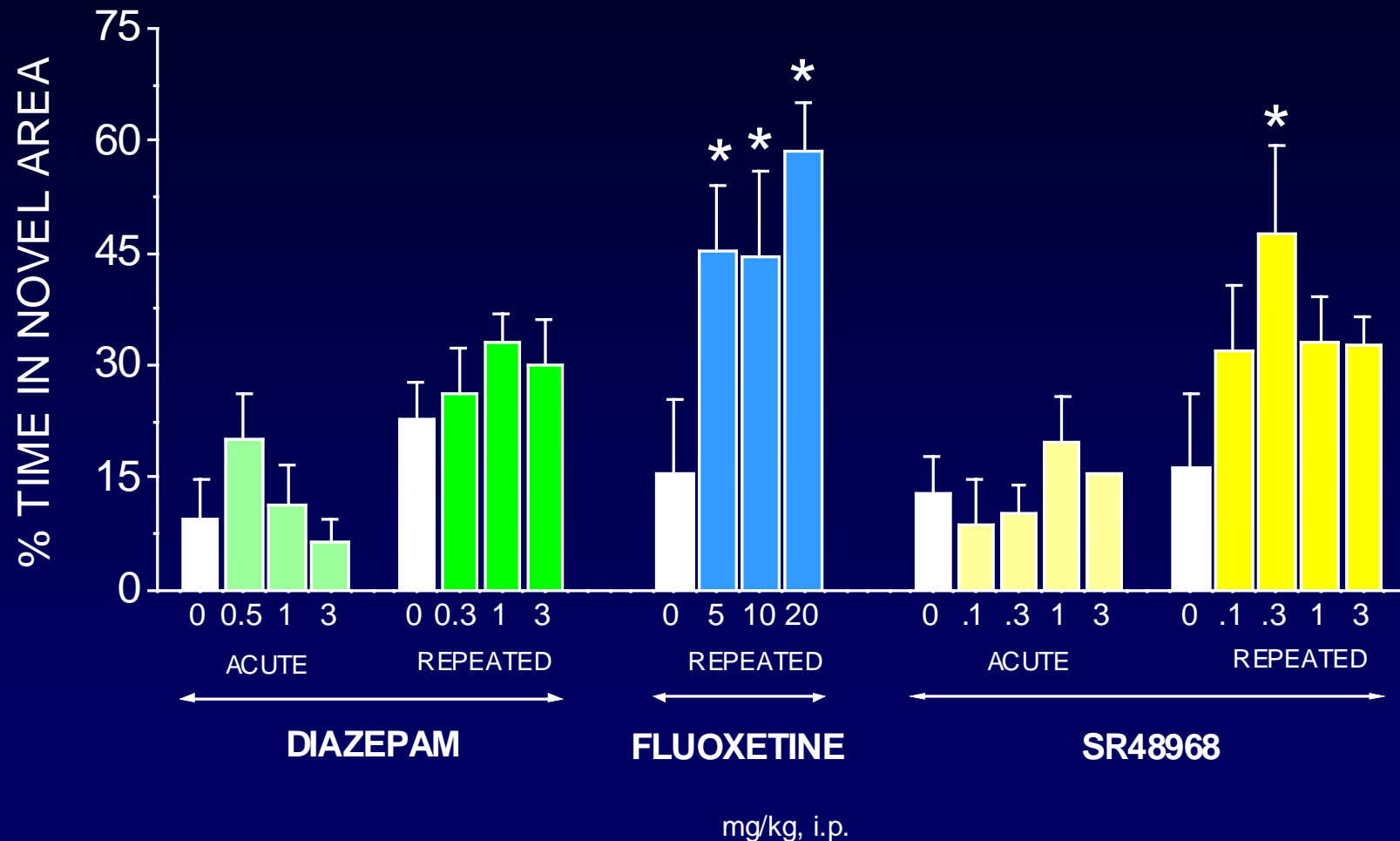


Free exploration test

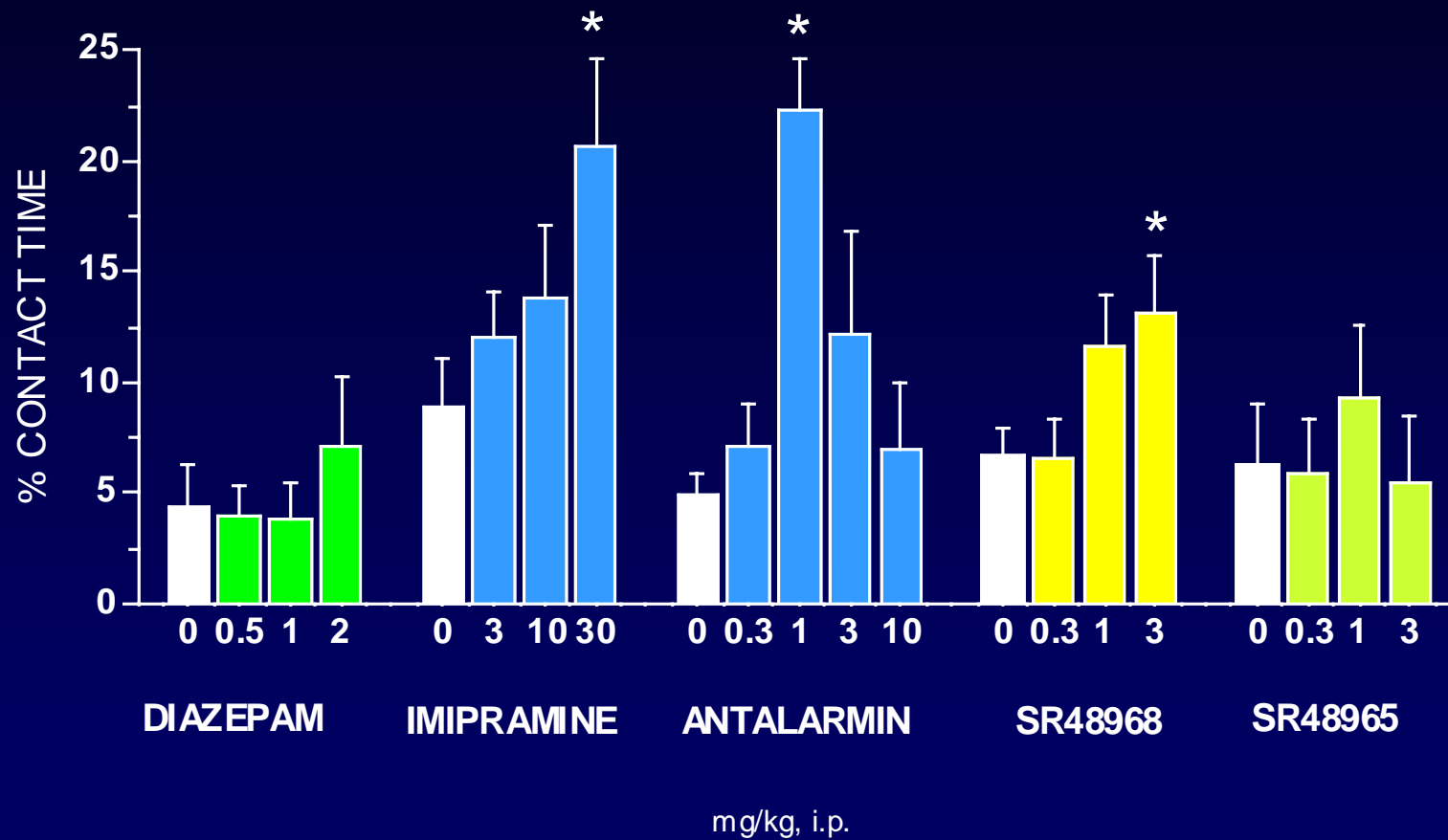


Staircase
test

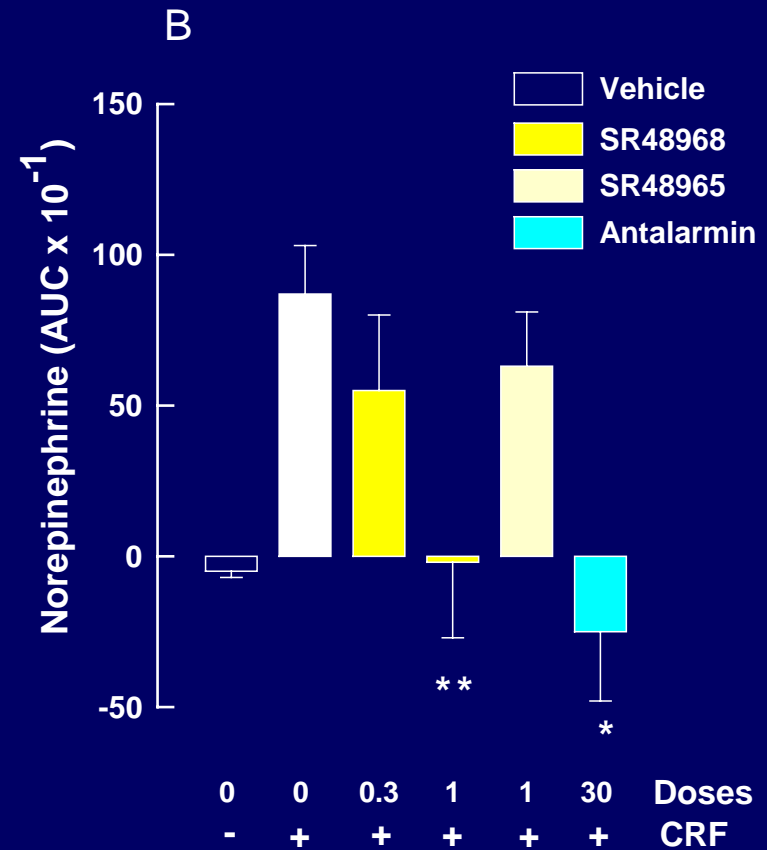
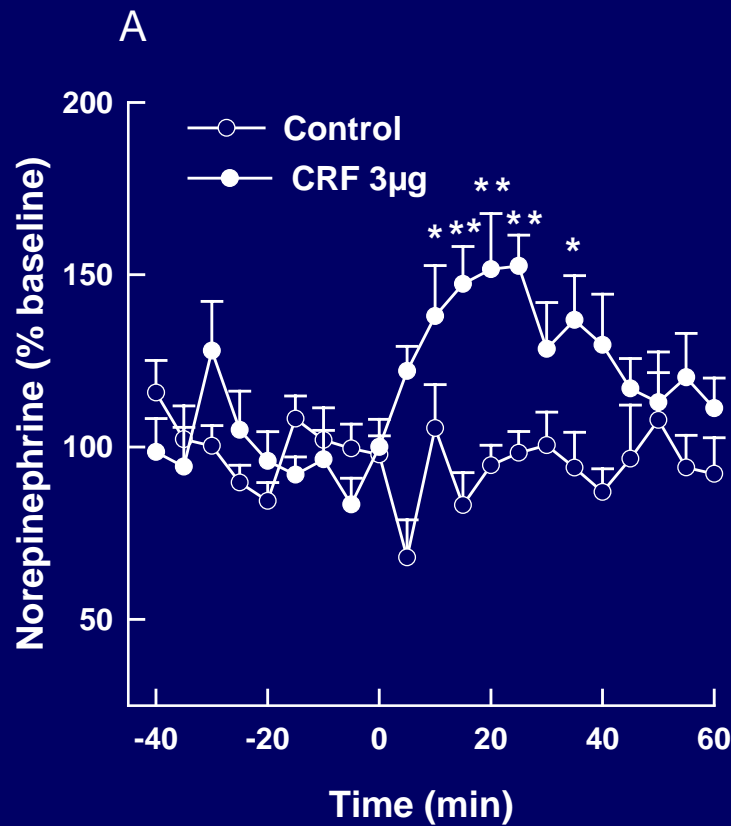
Effects of a selective NK₂ receptor antagonist on the behavior of mice in the free-exploration test following cat exposure



Effects of a selective NK₂ receptor antagonist on the behavior of rats in the staircase test following cat exposure

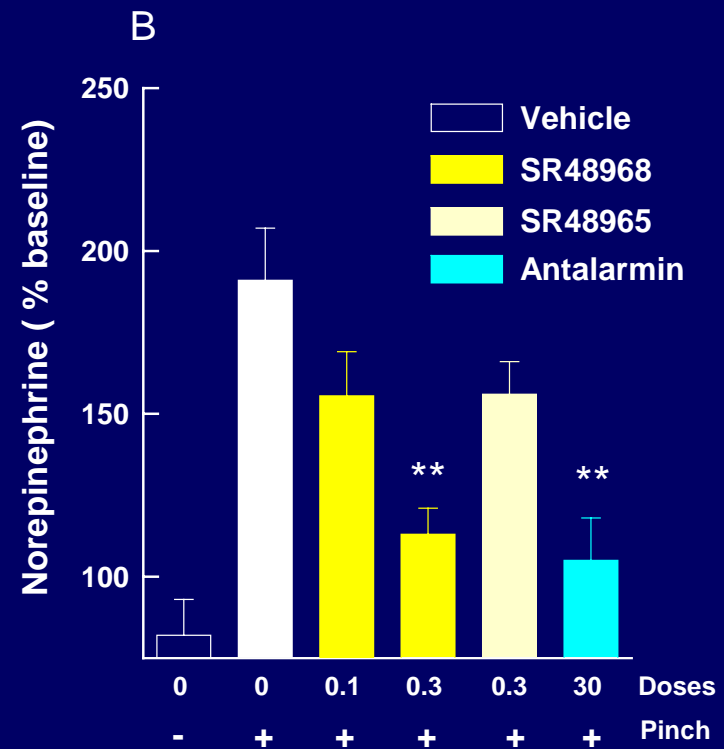
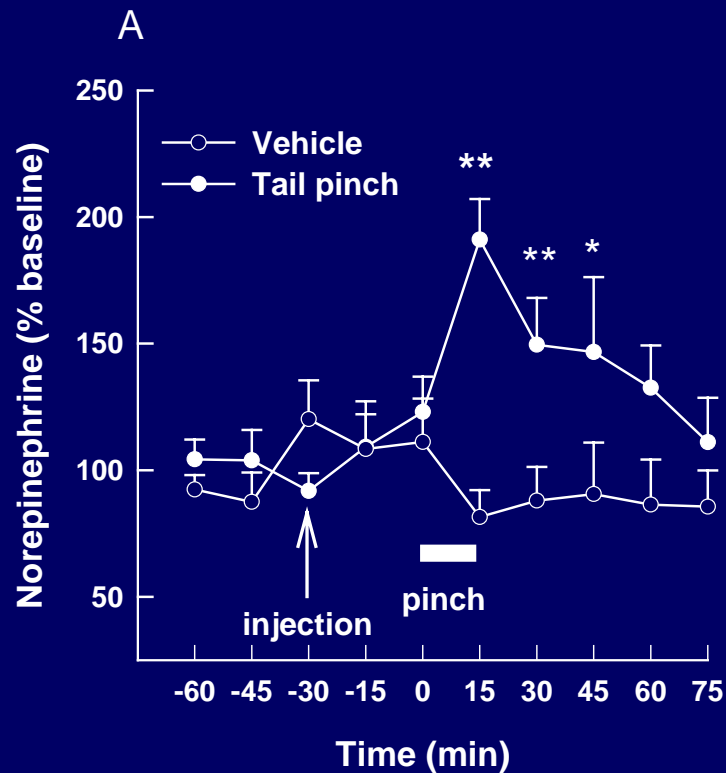


Effects of the selective NK₂ receptor antagonist SR48968 on CRF-induced release of NE in the prefrontal cortex of rats



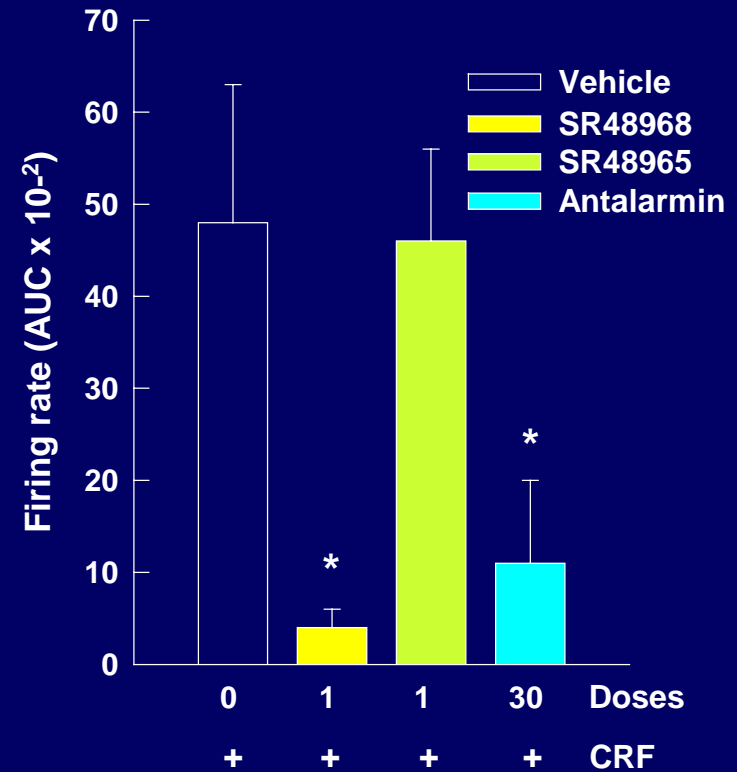
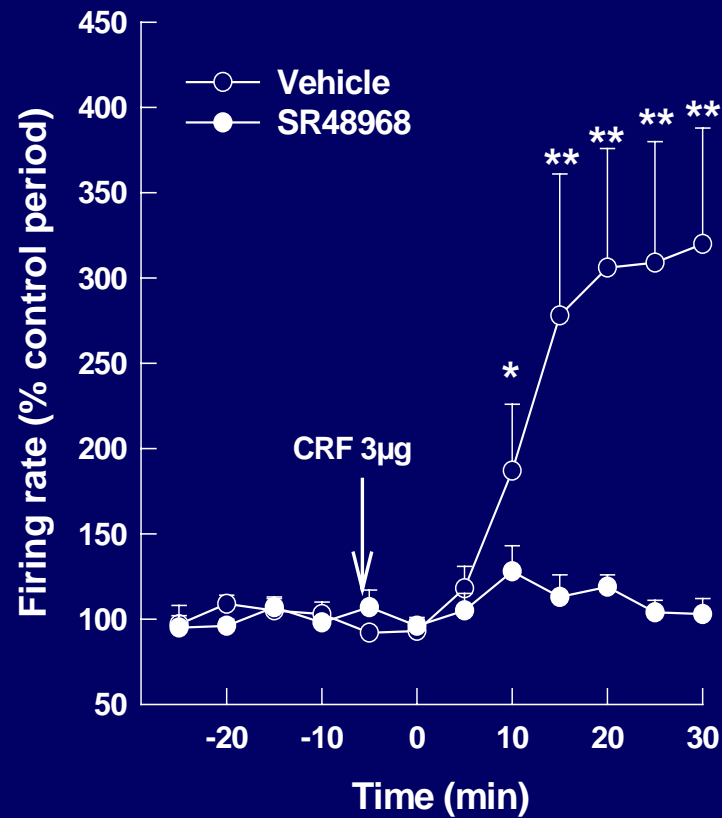
Steinberg et al.

Effects of the selective NK₂ receptor antagonist SR48968 on tail pinch-induced release of NE in the prefrontal cortex in rats



Steinberg et al.

Effects of the selective NK₂ receptor antagonist SR48968 on CRF-induced increase of firing in the locus coeruleus in rats



Steinberg et al.

NK₂ antagonists in models of anxiety-related disorders

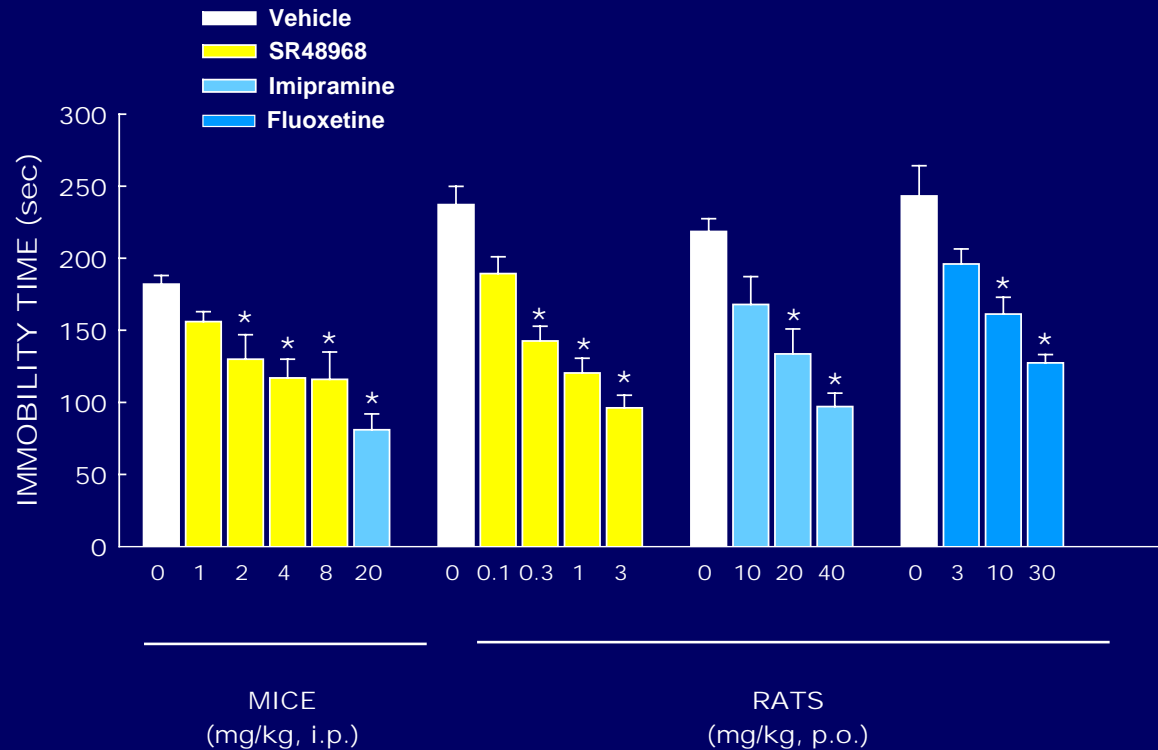
- ↙ **Show limited efficacy in models of anxiety sensitive to benzodiazepines**
- ↙ **Are active in situation involving unavoidable stressful stimuli or following traumatic stress exposure**
- ↙ **Show anti-CRF activity**

Do NK₂ receptor antagonists
have antidepressant-like
properties ?

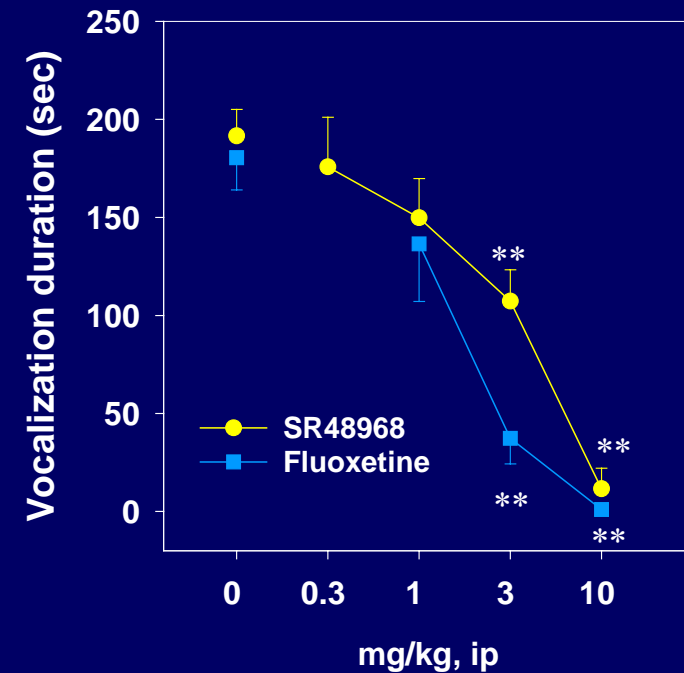
Evidence from behavioral and
neurochemical models of
depression in rodents

Effects of a selective NK₂ receptor antagonist in two screening models of depression

Forced-swimming test



Maternal separation-induced distress call in guinea-pig pups



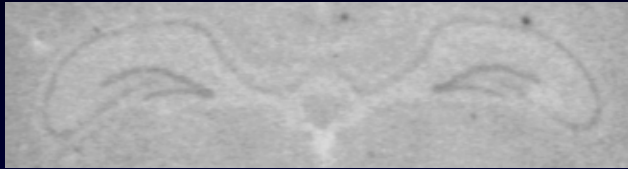
Steinberg et al.

Antidepressants and CREB expression

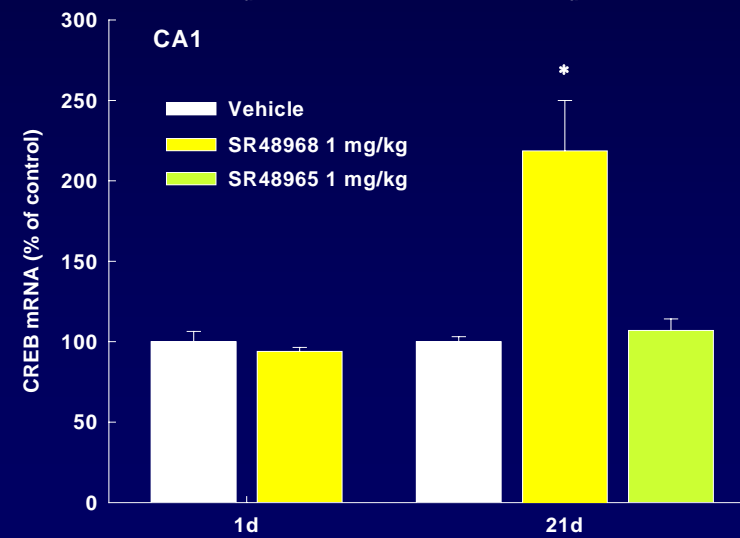
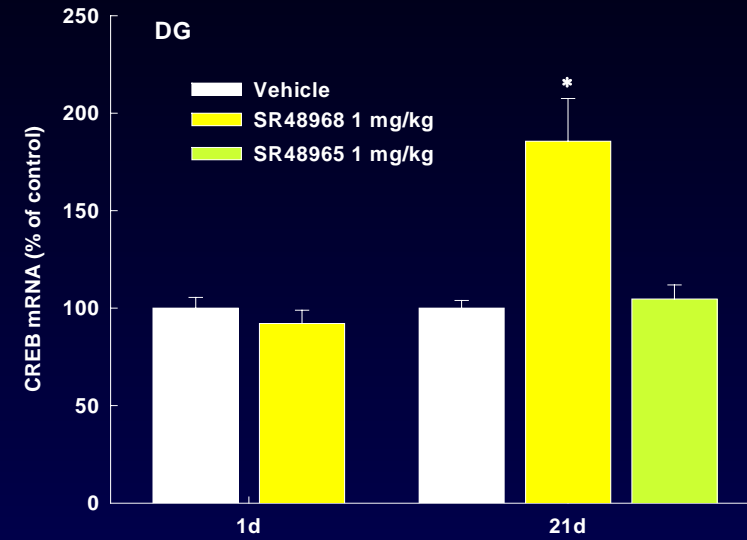
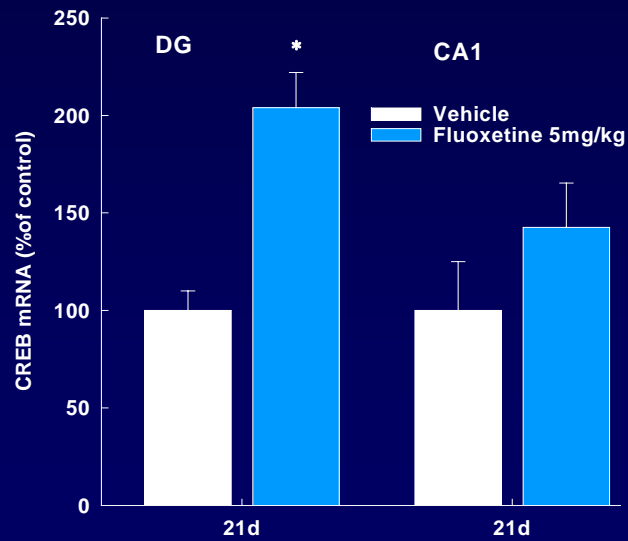
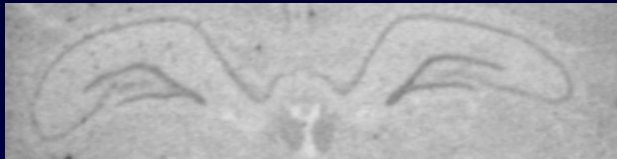
- ↙ **Studies in rodents have implicated the postreceptor components of the cAMP second messenger cascade in the action of different classes of antidepressants**
- ↙ **Chronic treatment with these drugs upregulated the cAMP system at several levels, including expression of the cAMP response-element binding protein (CREB) in the cerebral cortex and hippocampus**

Effects of a selective NK₂ receptor antagonist on CREB mRNA expression in rats

vehicle



SR48968



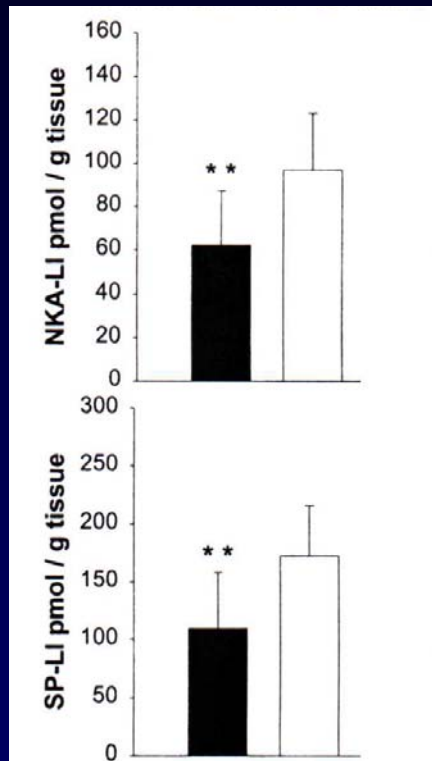
Steinberg et al.

SR48968 in models of depression

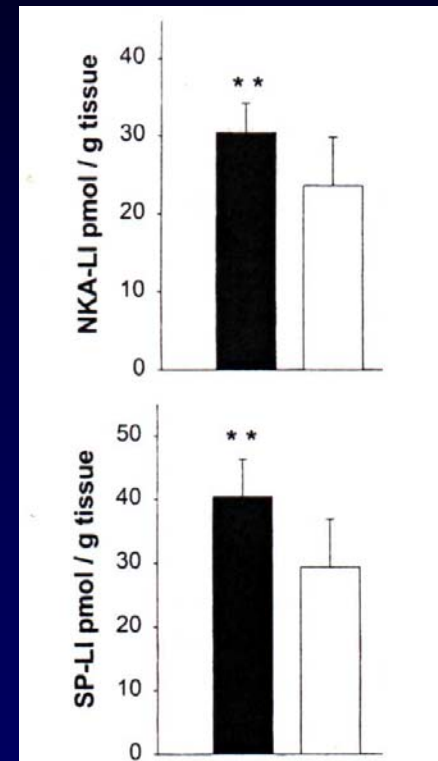
- ↙ Shows good activity in two behavioral models
- ↙ Sustained blockade of NK₂ receptors leads to an upregulation of the expression of CREB mRNA in the hippocampus, as do antidepressants

NKA-like immunoreactivity (Li) and substance P (SP-Li) are modified in FSL compared to control rats

STRIATUM



FRONTAL CORTEX

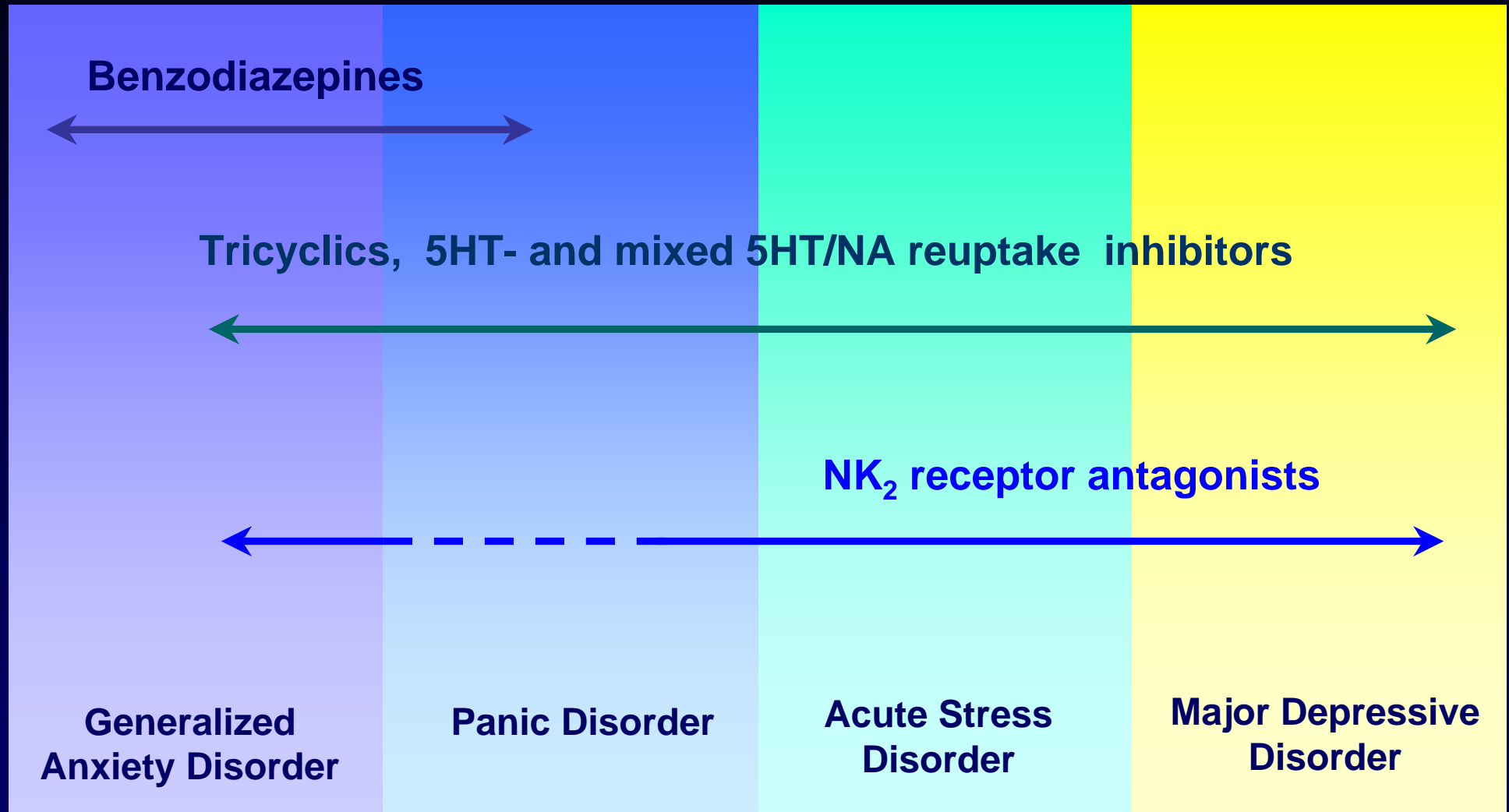


Husum et al. Neuropharmacology 24 : 183-91, 2001

OVERALL SUMMARY

- ↙ **Studies using classical anxiety models yielded inconsistent data with NK₂ antagonists**
- ↙ **Unlike benzodiazepines, NK₂ antagonists were active in situations involving traumatic stress or unavoidable contact with threatful stimuli**
- ↙ **The NK₂ antagonist SR48968 showed clear antidepressant-like activity**

Expected clinical spectrum of therapeutic activity of NK₂ antagonists in anxiety/depressive disorders



Acknowledgements

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- **Anatomical studies**

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- **Neurochemical studies**

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