RATIONALE FOR DEVELOPMENT OF NK_2 ANTAGONISTS AS ANXIOLYTICS AND ANTIDEPRESSANTS

?

1990

2000

« No apparent expression of SKR (NK_2) mRNA in the CNS »

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

First clinical trial (Phase IIa) with a selective NK_2 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]

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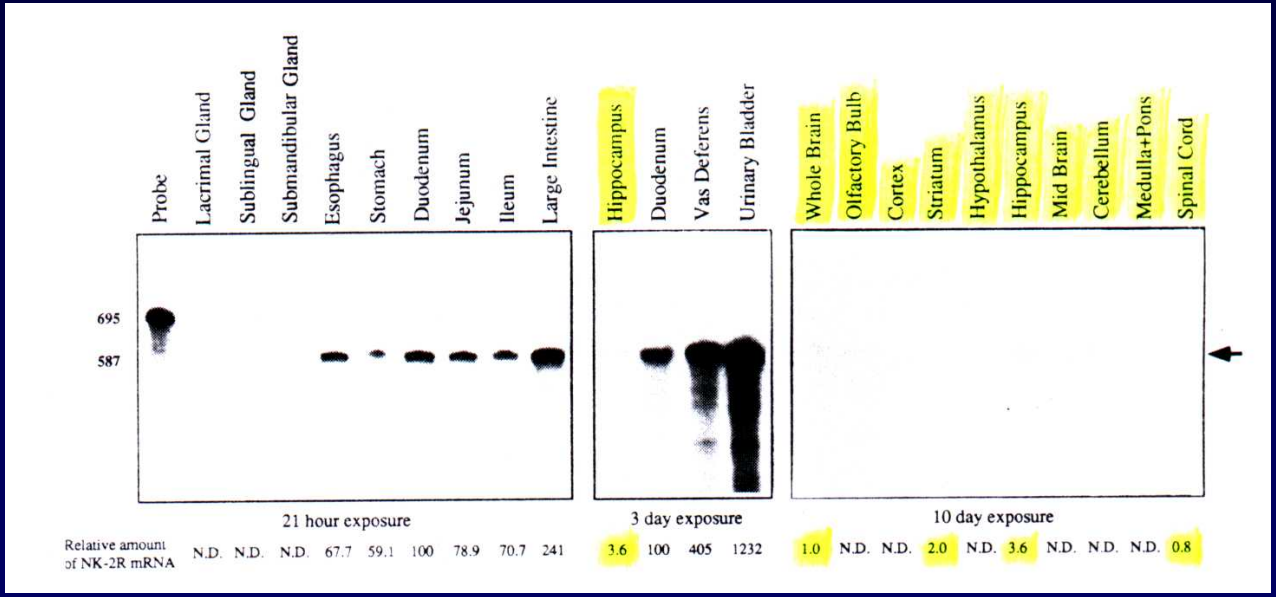
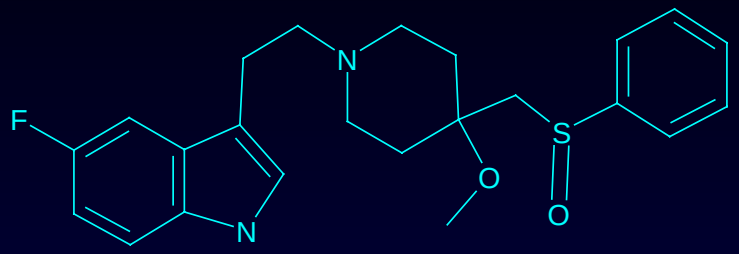


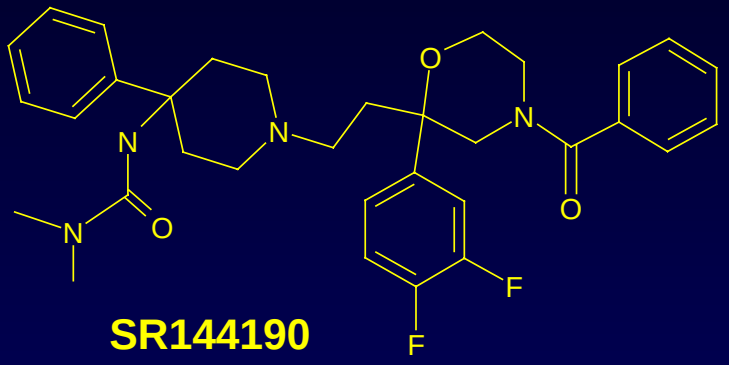
Ann. N.Y. Acad. Sci. 632 : 479-82, 1991

Selective and potent non-peptide NK_2 receptor antagonists

SR48968



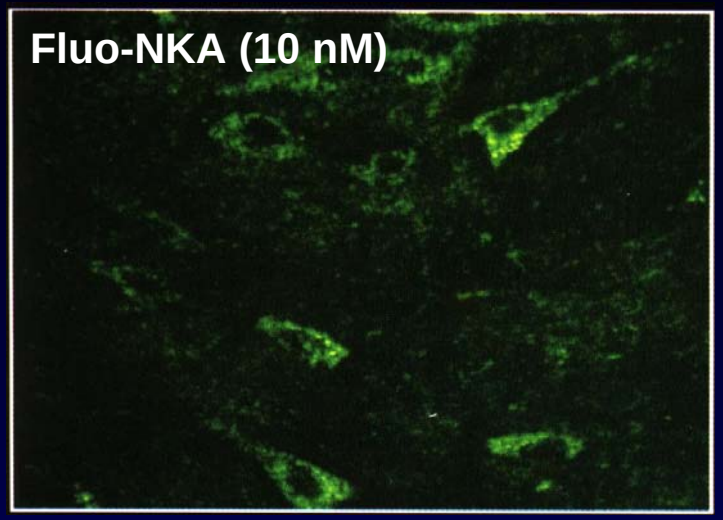
GR159897

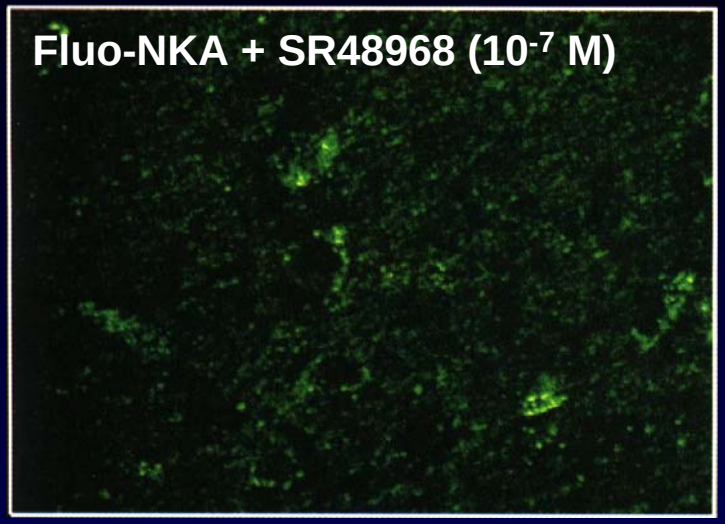


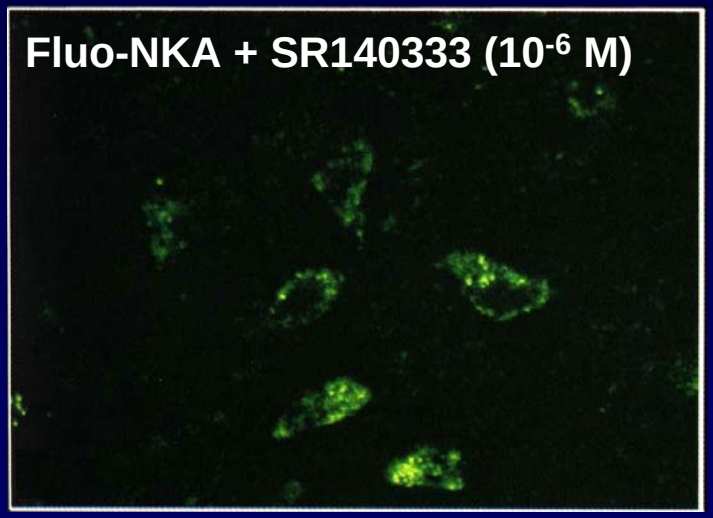
SR144190

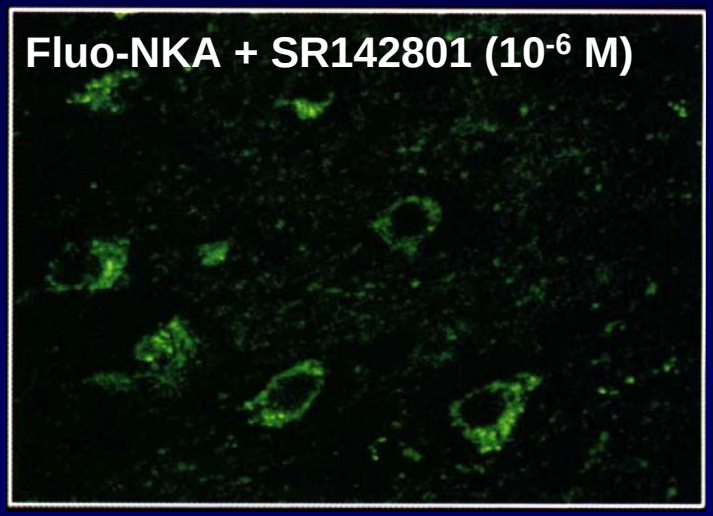
	hNK$_2$-CHOpKi	pA$_2$	
GR159897	9.5	8.72	Beresford et al. (1995)
SR48968	9.9	10.3	Emonds-Alt et al. (1992)
SR144190		10.1	Emonds-Alt et al. (1997)

Evidence of the presence of NK_2 binding sites in the septal area of rats using a fluorescent-tagged neurokinin A (NKA) derivative



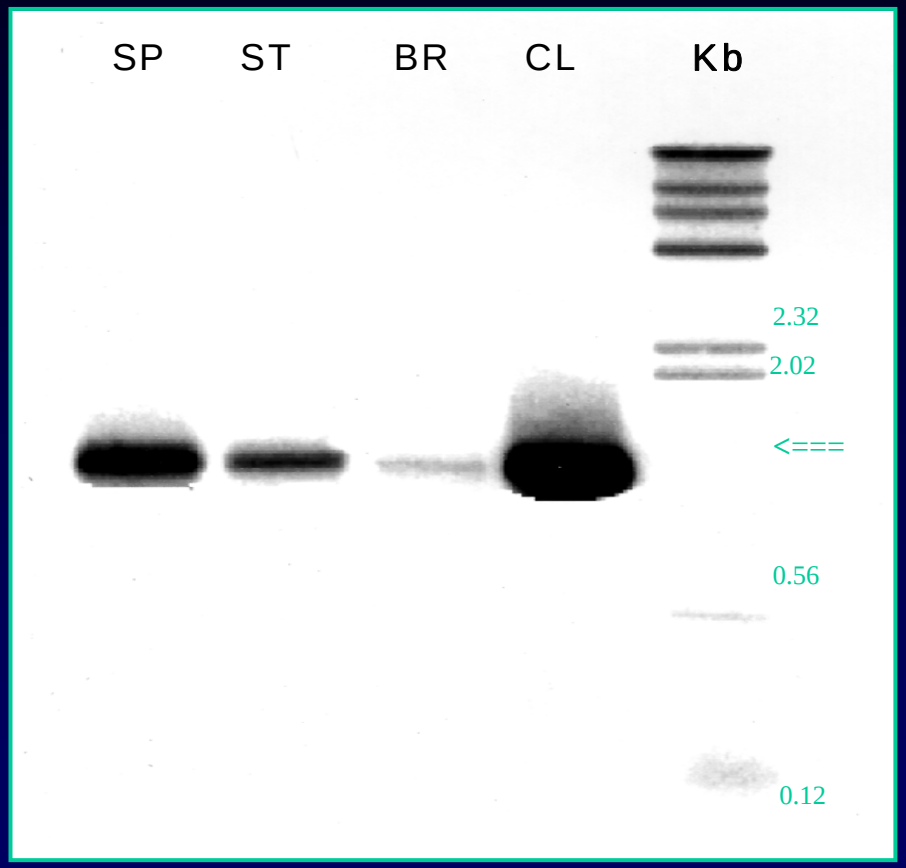






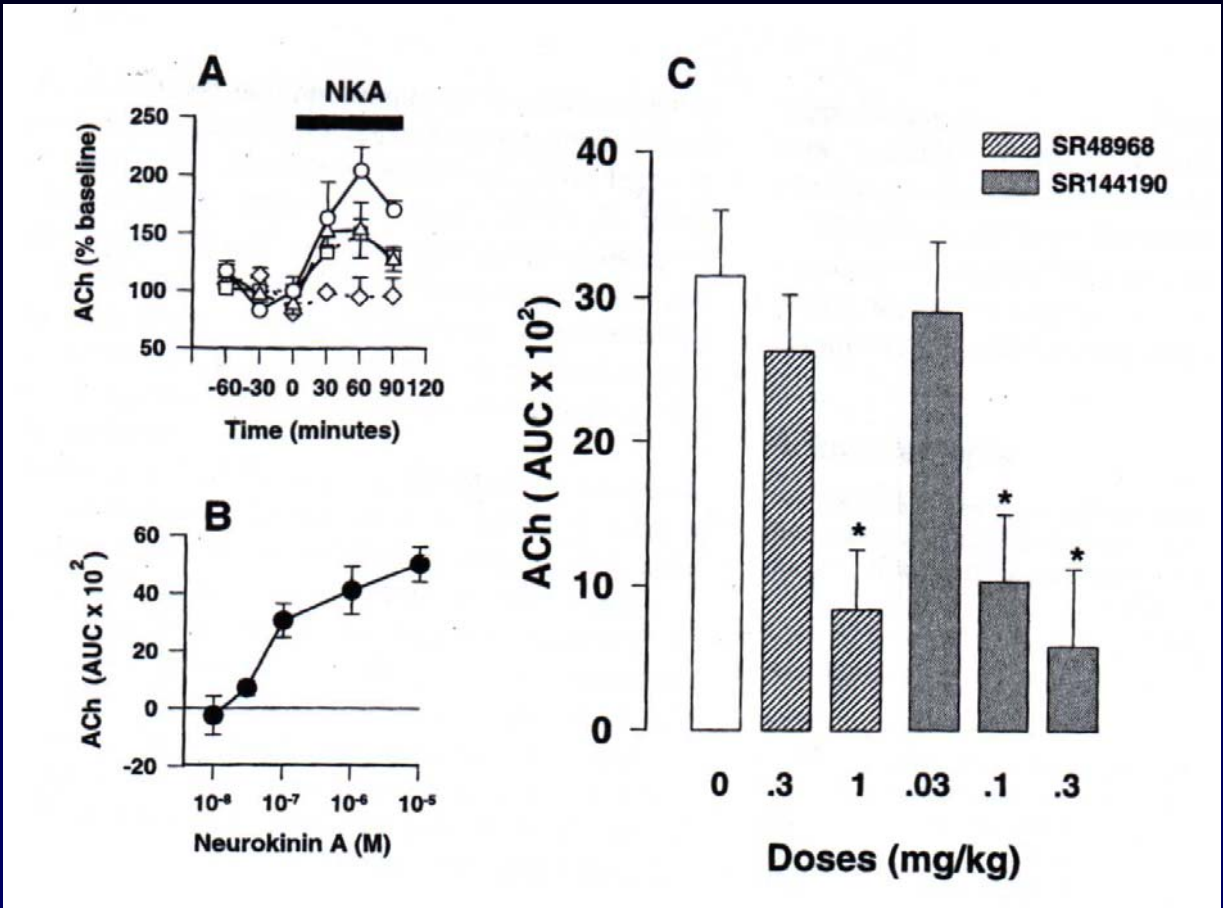
Steinberg et al. Eur. J. Neurosci. 10 : 2337-45, 1998

Analysis by RT-PCR of NK_2 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

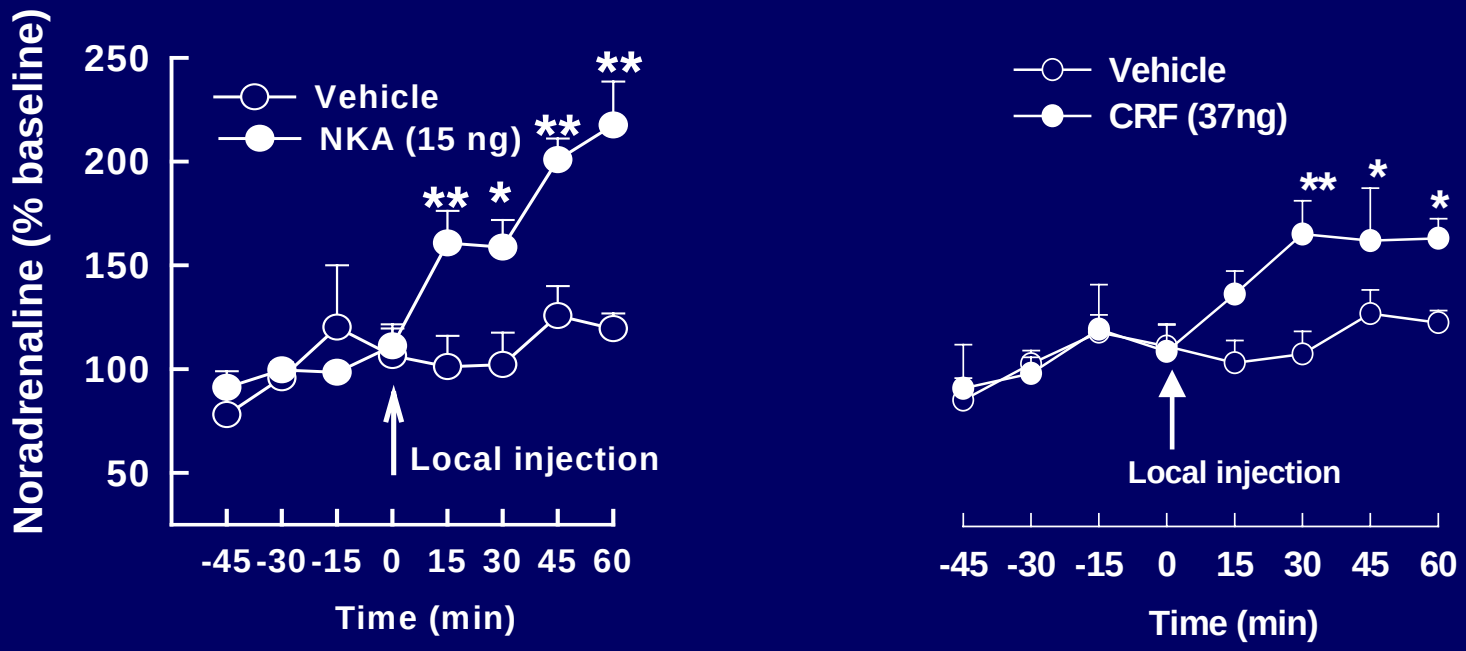
Structure and properties of rat tachykinin receptors

	NK_1	**NK_2**	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+}	**IP_3-Ca^{2+}**	IP_3-Ca^{2+}
Expression Sites			
Nervous system	+++	**+**	+++
Peripheral tissues	+++	**++**	+++

Does central infusion of the preferred NK_2 endogenous peptide NKA modulate stress response?

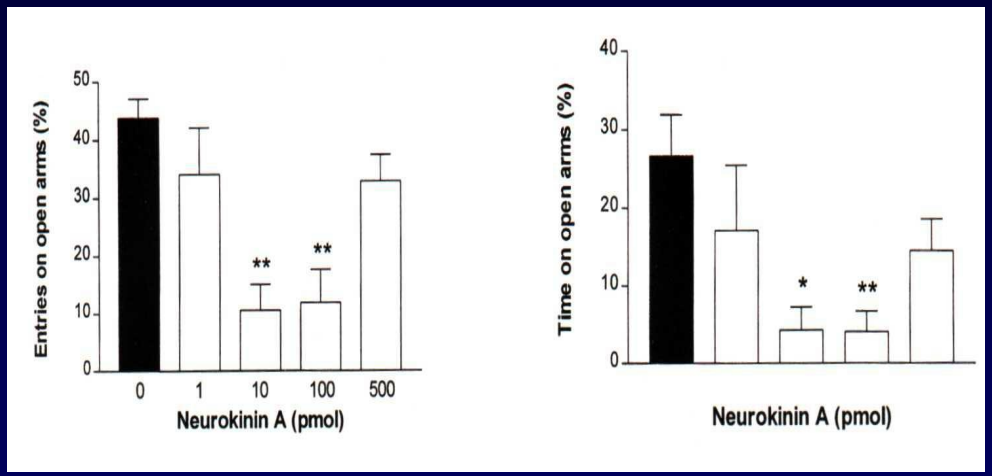
Evidence from neurochemical and behavioral studies

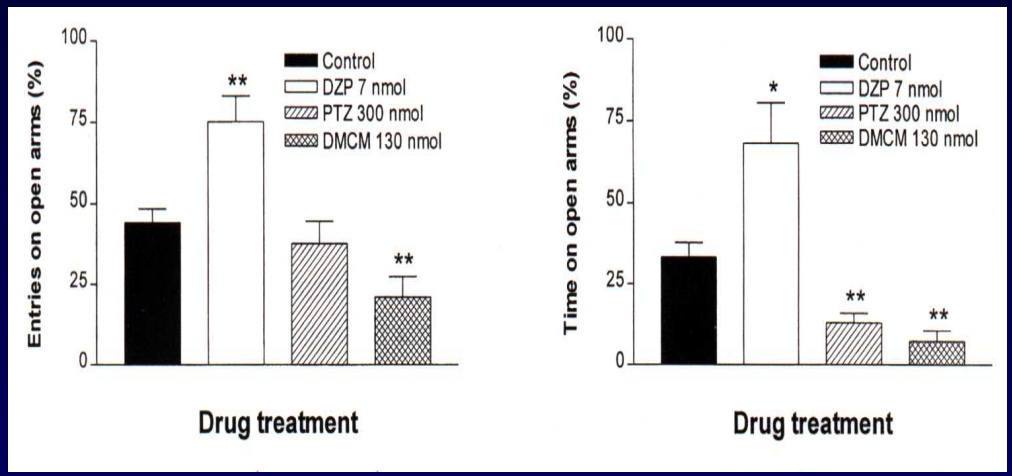
Effects of neurokinin A and CRF microinfused into the locus coeruleus on prefrontal cortex NE release



Steinberg et al.

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





Teixeira et al. Eur. J. Pharmacol. 311 : 7-14, 1996

Do selective NK_2 receptor antagonists modulate emotional behaviors ?

Animal models used to investigate the effects of NK_2 receptor antagonists on emotional processes

- Punished lever pressing
- Punished drinking
- Elevated plus-Maze
- Light-dark box
- Marmoset human intruder response

- Mouse defense test battery

- Free-exploration box
- Staircase test after cat exposure
- Stress-induced increase of NE activity

- Forced swimming
- Maternal separation-induced vocalizations
- CREB mRNA expression

?

Generalized Anxiety Disorder

Panic Disorder

Acute Stress Disorder

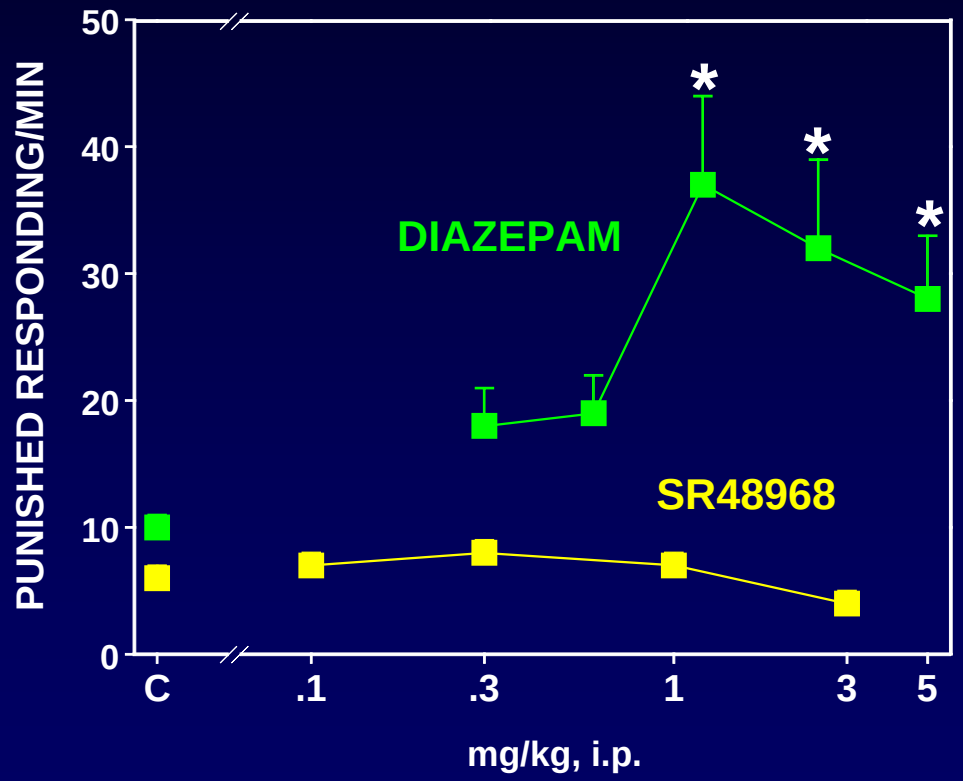
Major Depressive Disorder

Do NK_2 receptor antagonists have anxiolytic-like properties ?

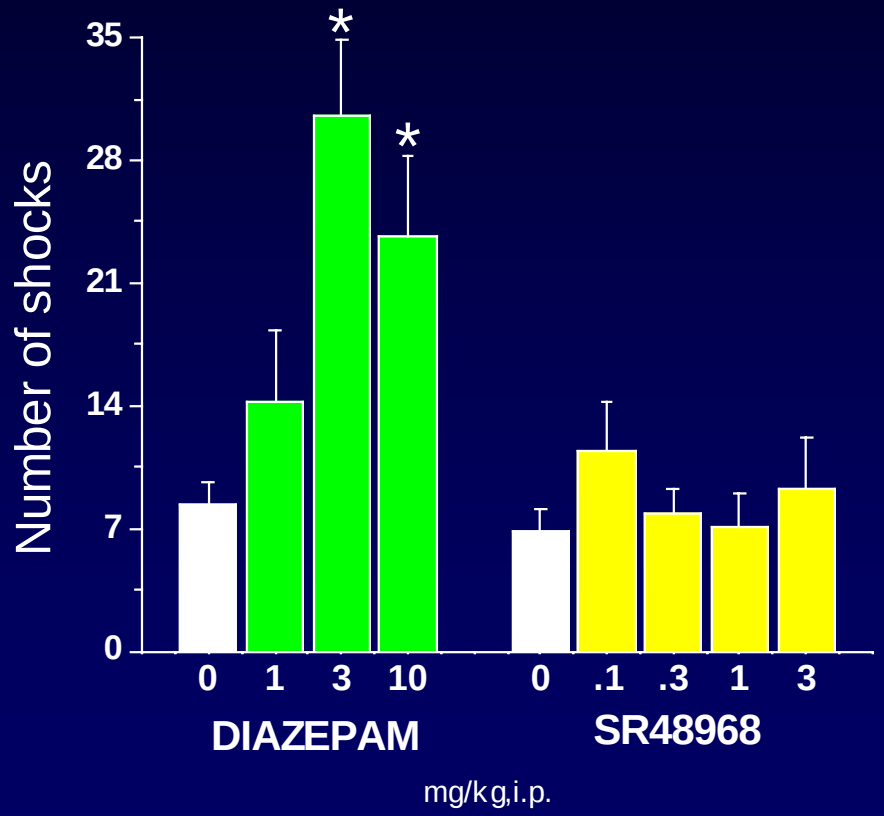
Evidence from behavioral and neurochemical models of anxiety/stress disorders

Effects of a selective NK_2 receptor antagonist in two traditional conflict models in rats

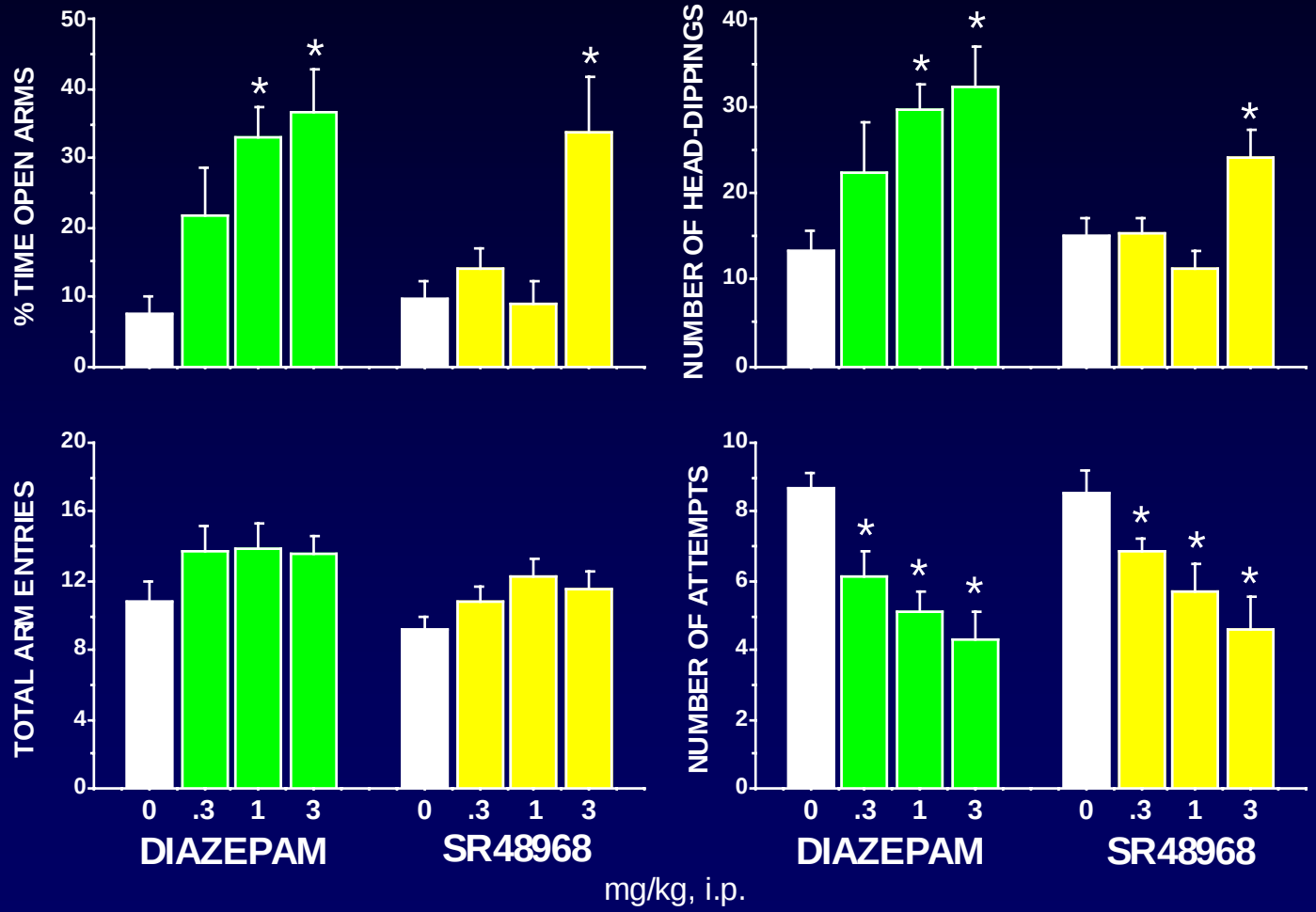
Punished lever pressing test



Punished drinking test

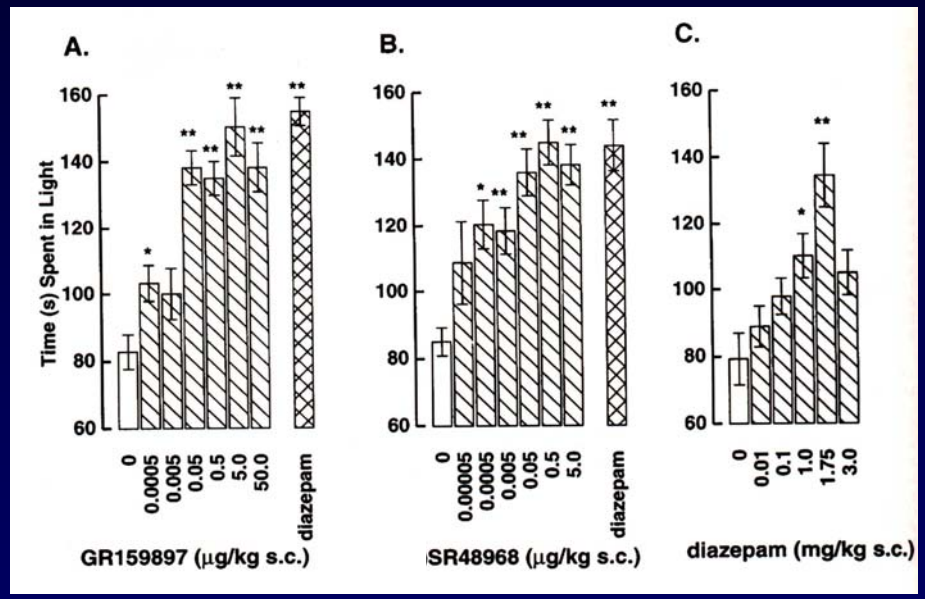


Effects of a selective NK_2 receptor antagonist in the elevated plus-maze test in rats

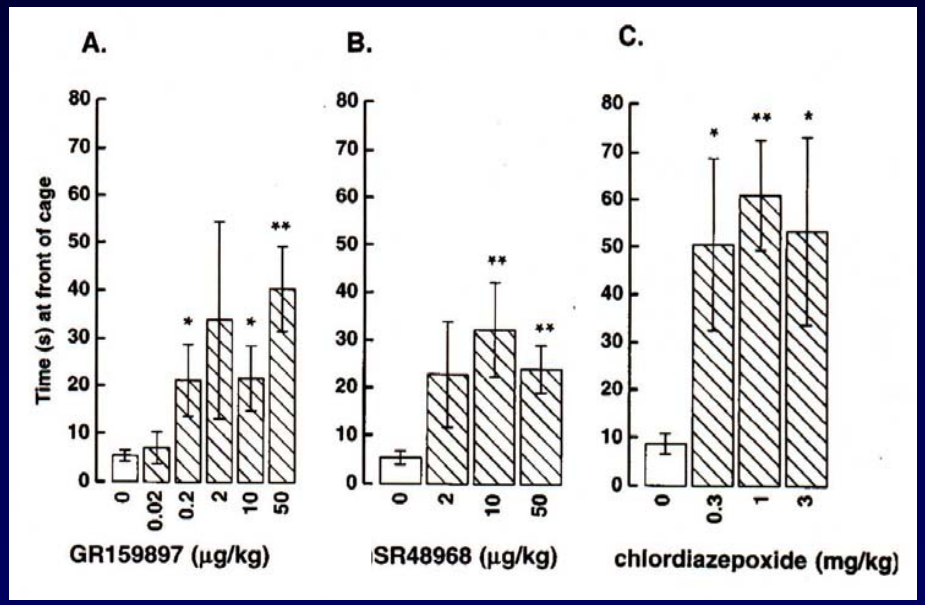


Effects of selective NK_2 receptor antagonists in animal models of anxiety

Mouse light-dark box



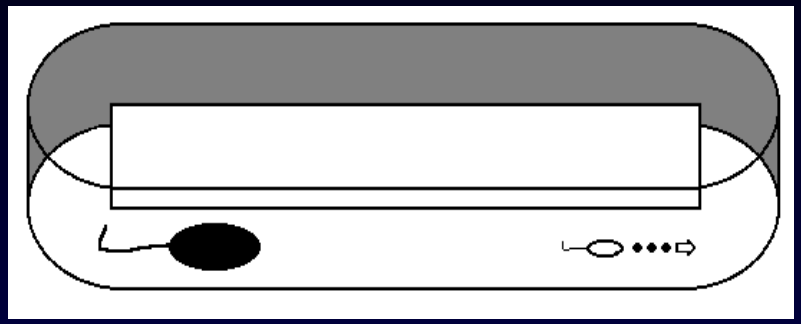
Marmoset human intruder response test



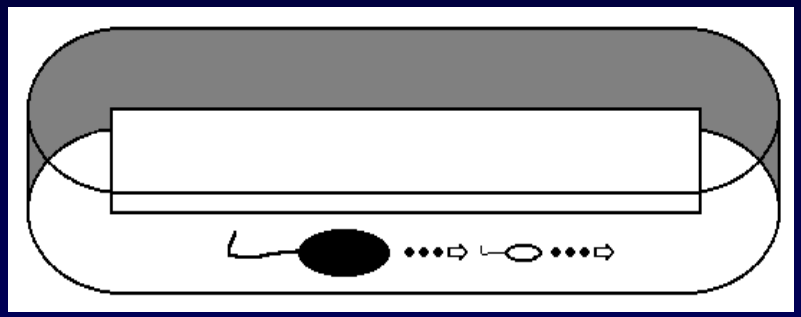
Walsh et al., Psychopharmacology 121 : 186-91, 1995

The mouse defense test battery

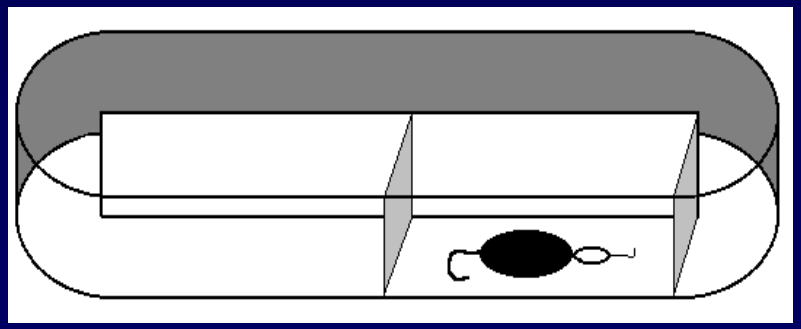
FLIGHT



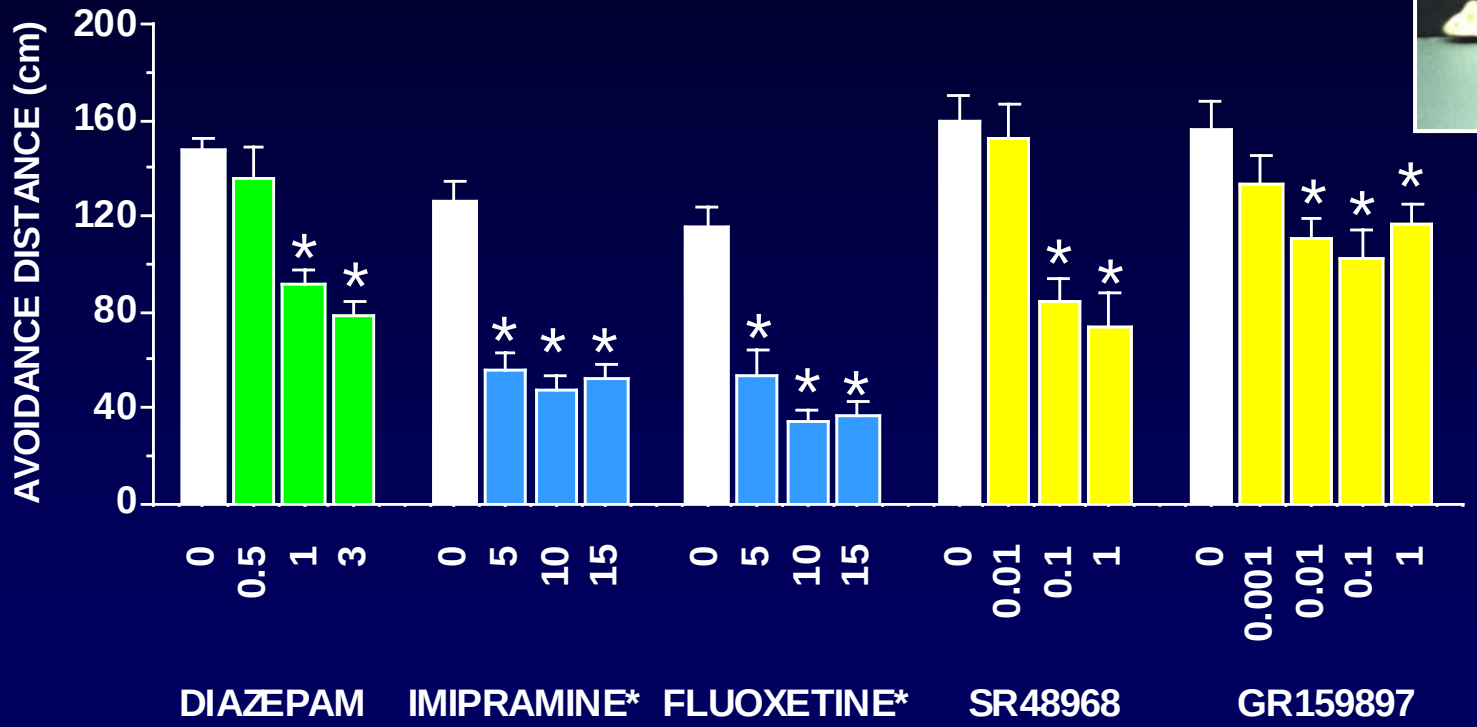
RISK ASSESSMENT



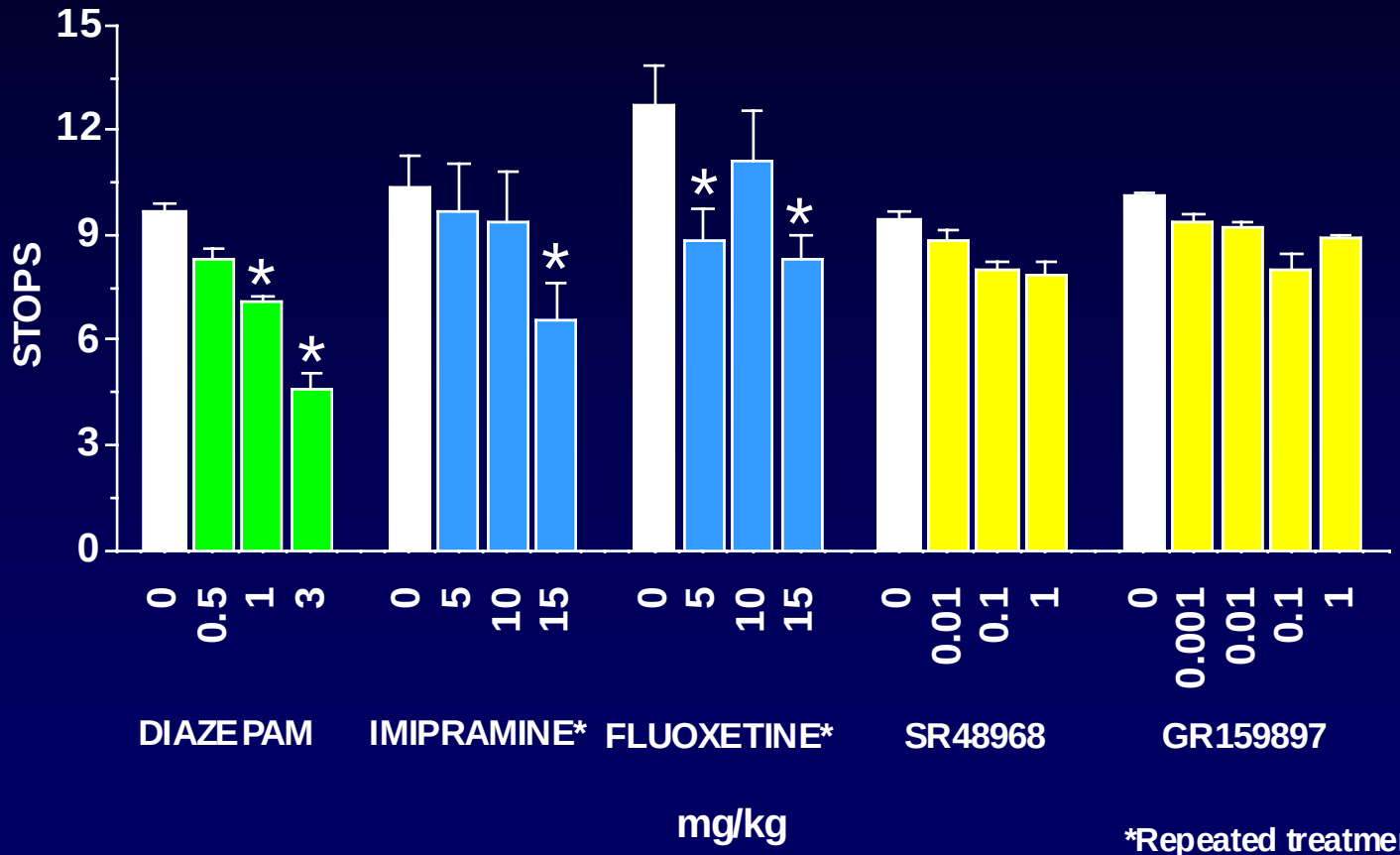
DEFENSIVE AGGRESSION



Effects of selective NK_2 receptor antagonists on flight behavior in the mouse defense test battery

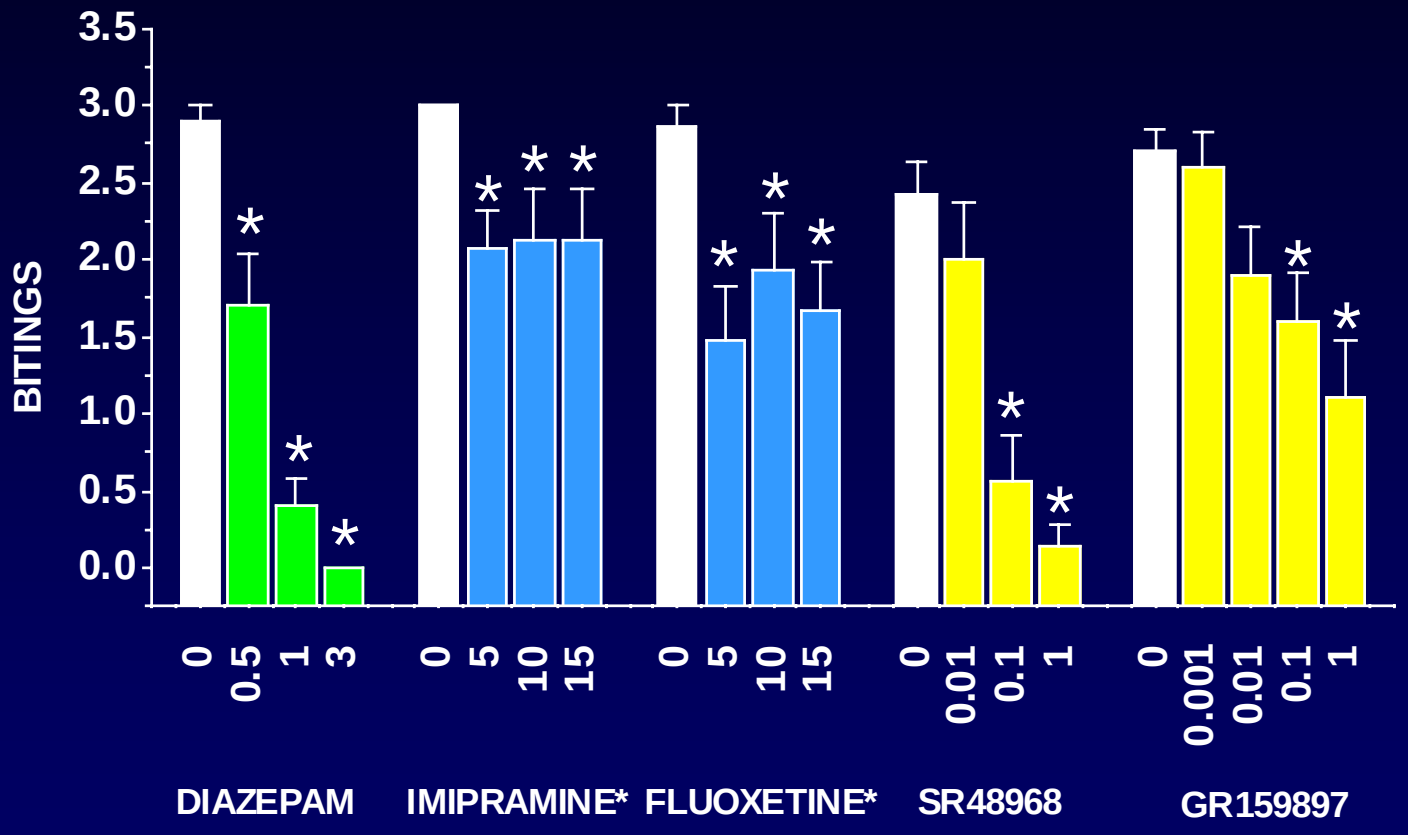


Effects of selective NK_2 receptor antagonists on risk assessment behavior in the mouse defense test battery



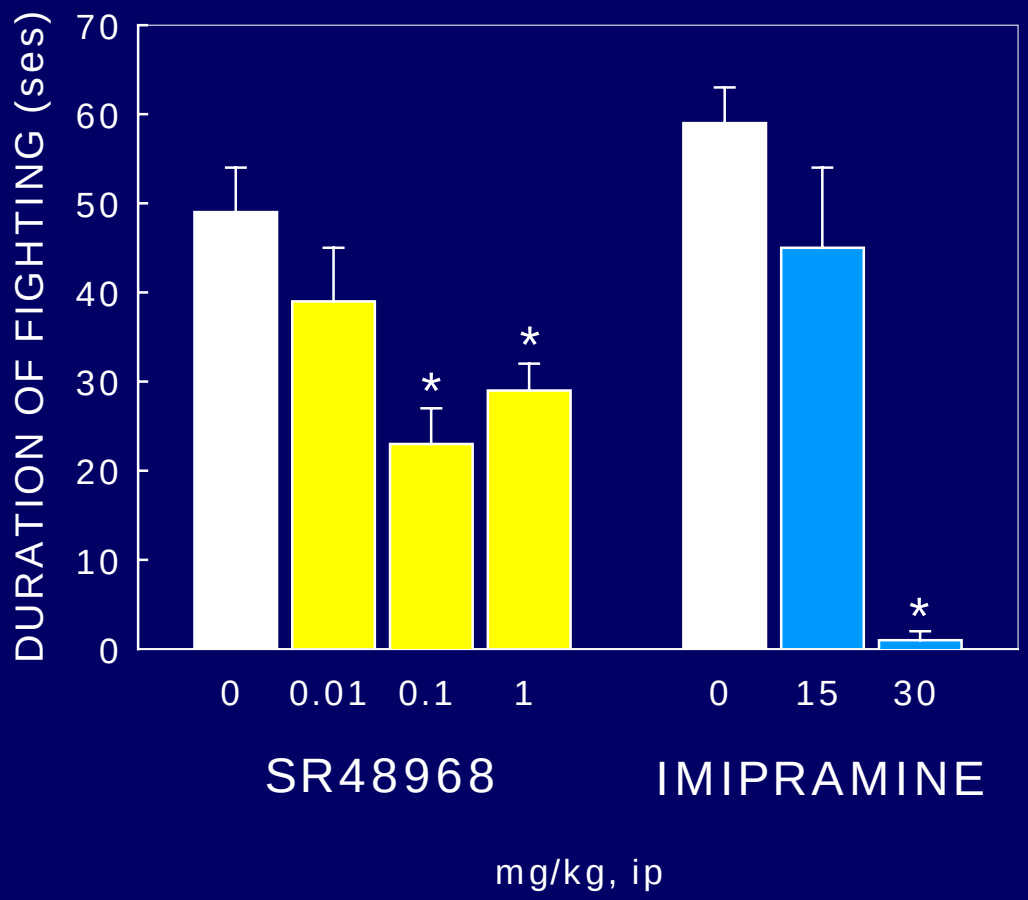
*Repeated treatment

Effects of selective NK_2 receptor antagonists on defensive aggression in the mouse defense test battery



*Repeated treatment

Effects of a selective NK_2 receptor antagonist on isolation-induced aggression in mice



Investigation of the behavior of rodents following cat exposure

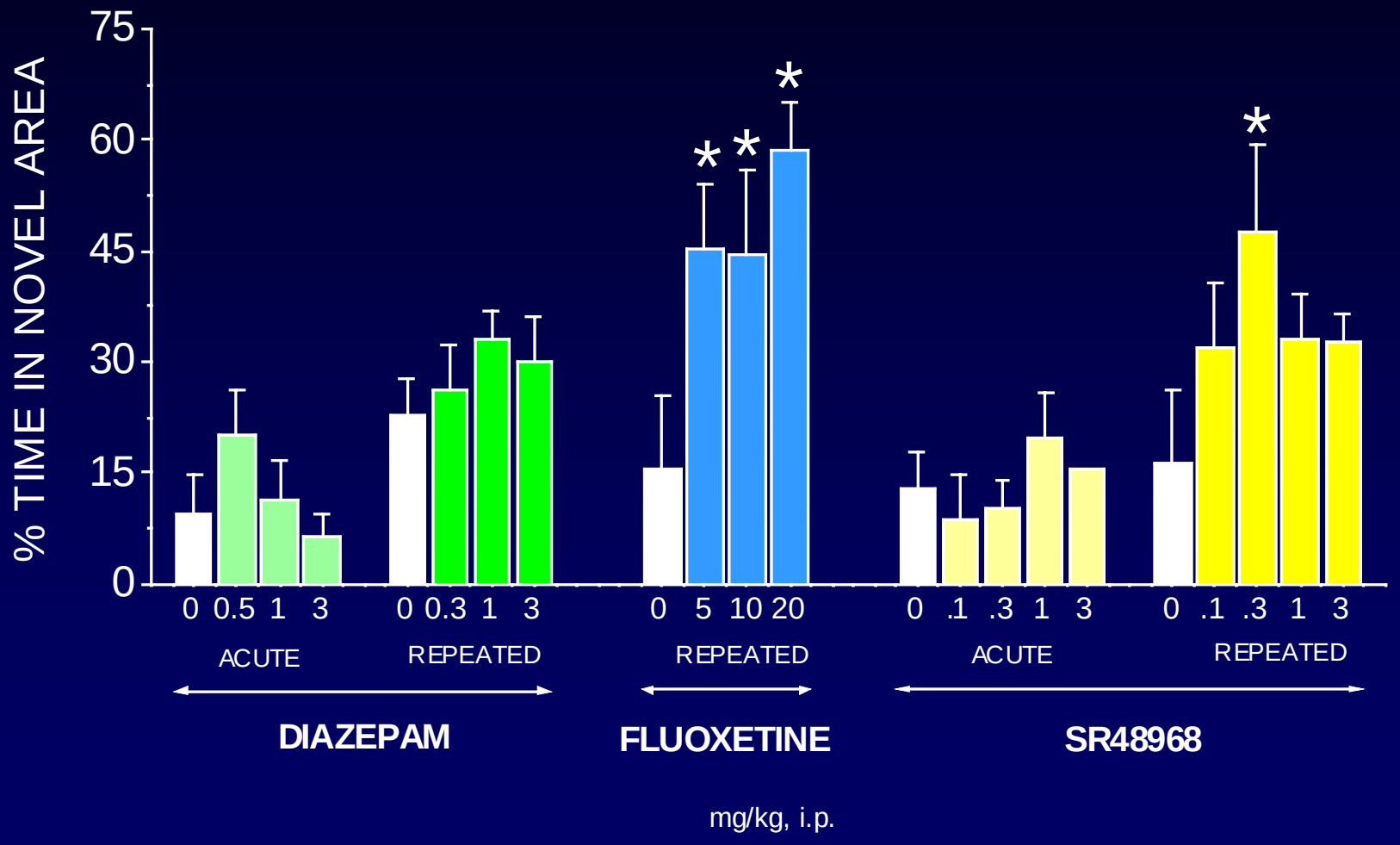
Cat exposure (5-10 min)

60 min

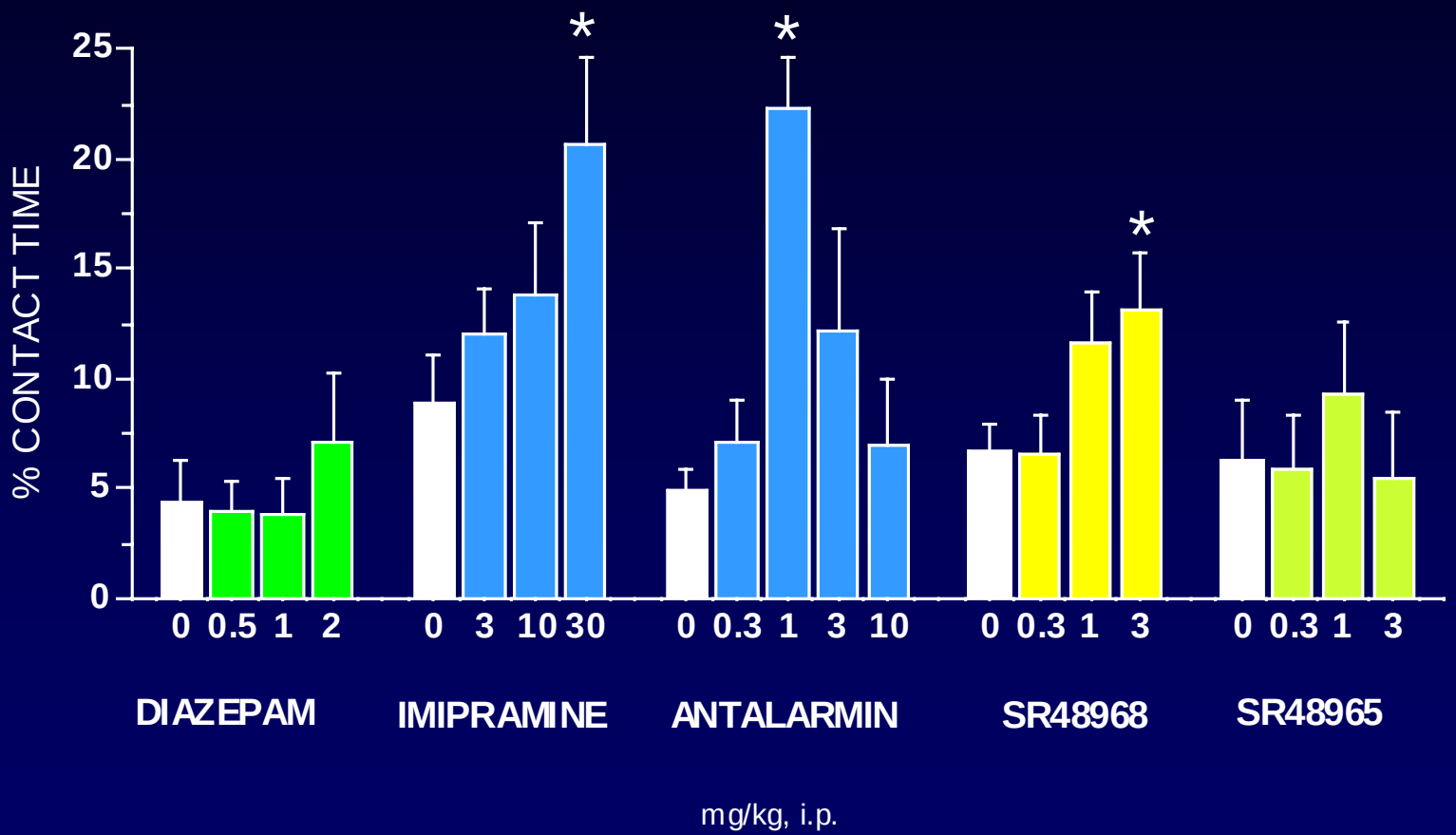
Free exploration test

Staircase test

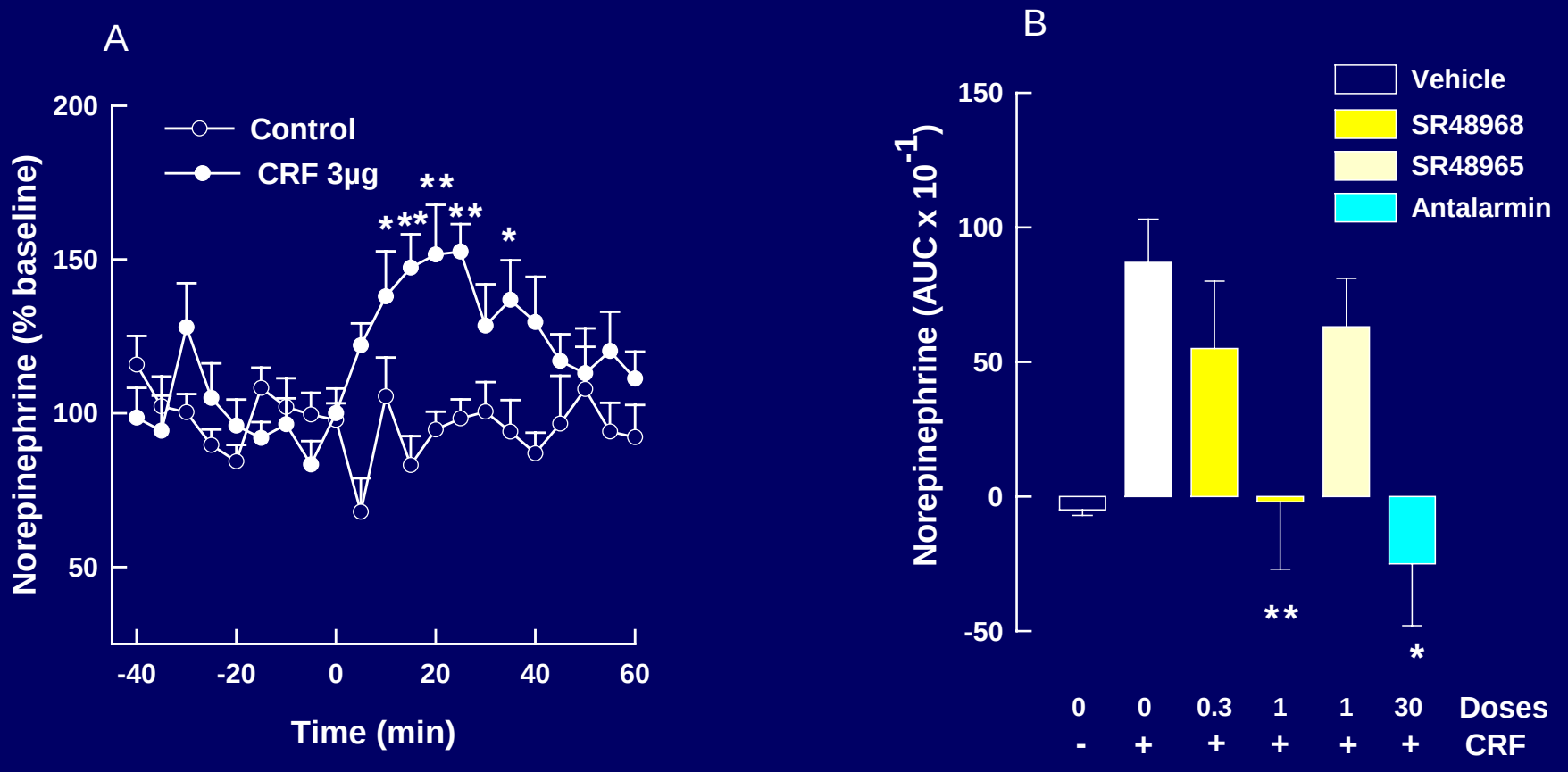
Effects of a selective NK_2 receptor antagonist on the behavior of mice in the free-exploration test following cat exposure



Effects of a selective NK_2 receptor antagonist on the behavior of rats in the staircase test following cat exposure

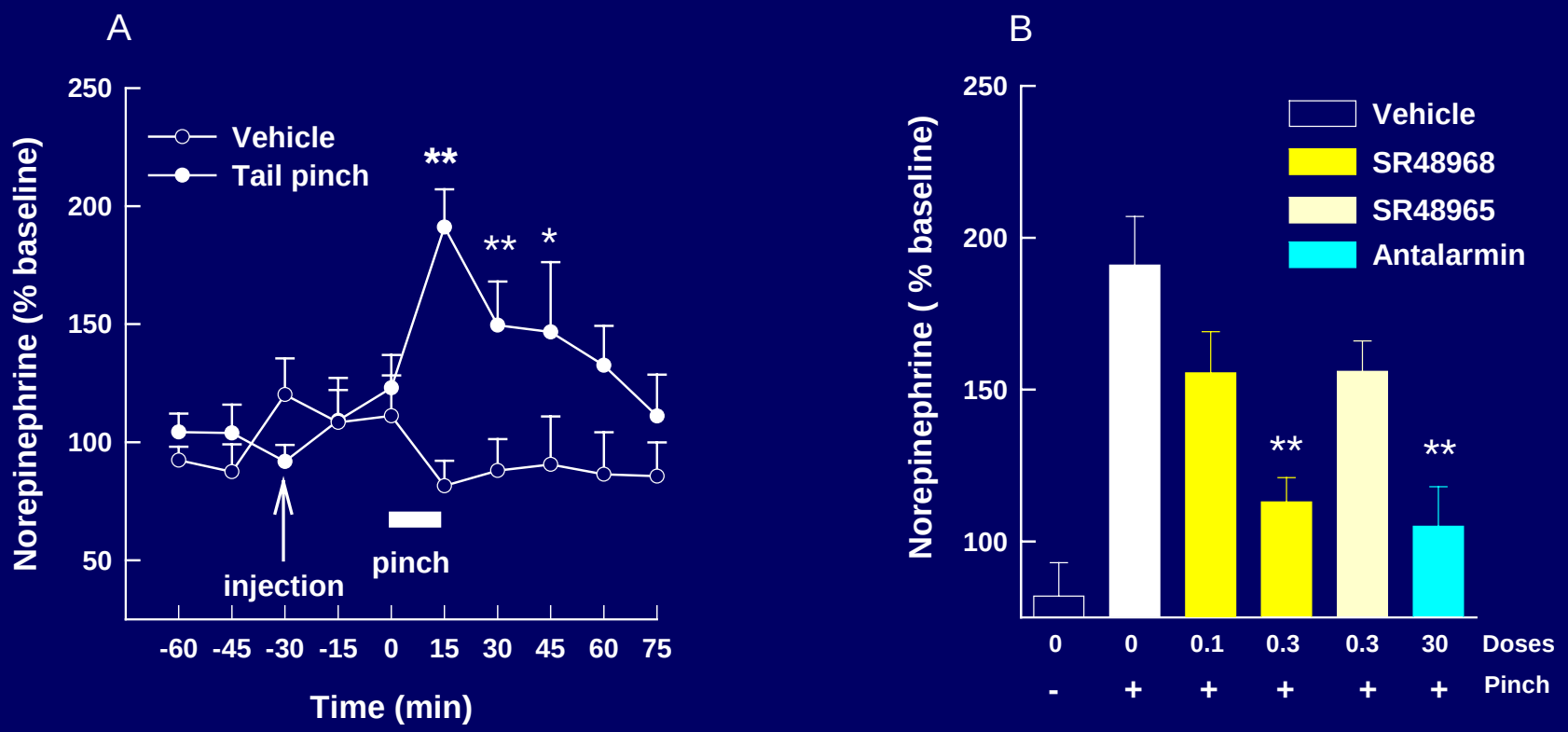


Effects of the selective NK_2 receptor antagonist SR48968 on CRF-induced release of NE in the prefrontal cortex of rats



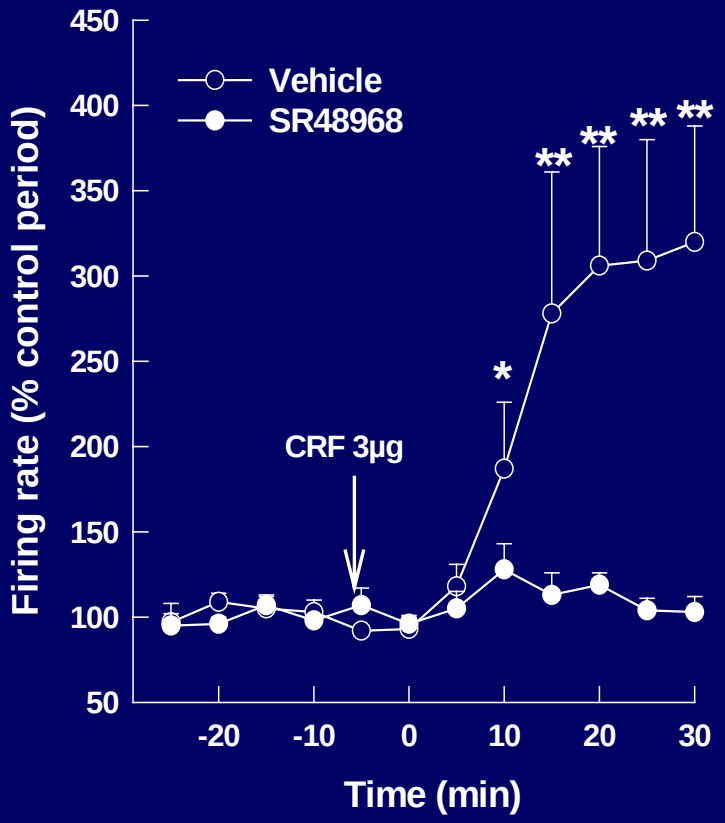
Steinberg et al.

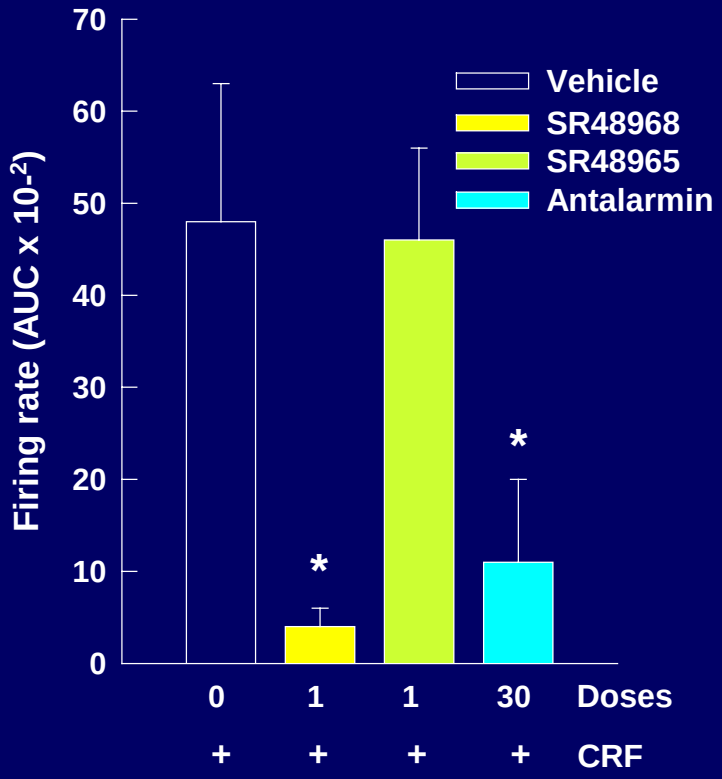
Effects of the selective NK_2 receptor antagonist SR48968 on tail pinch-induced release of NE in the prefrontal cortex in rats



Steinberg et al.

Effects of the selective NK_2 receptor antagonist SR48968 on CRF-induced increase of firing in the locus coeruleus in rats





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NK_2 antagonists in models of anxiety-related disorders

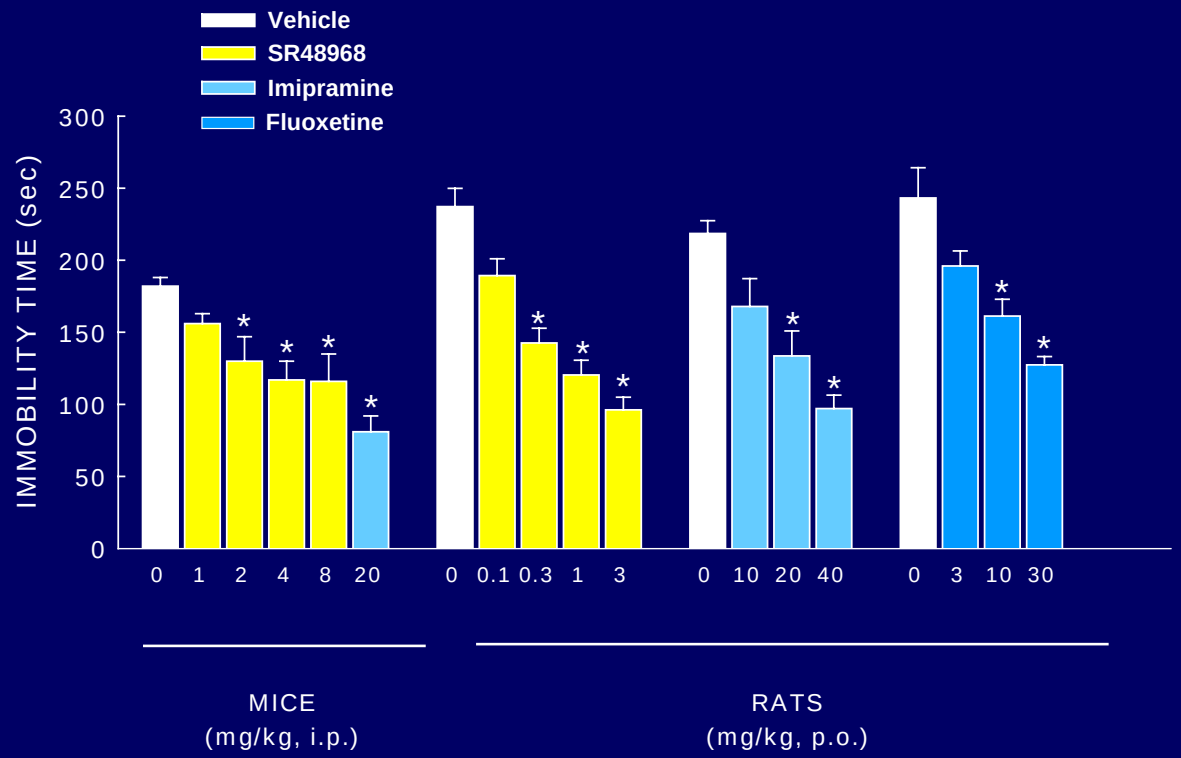
- **Show limited efficacy in models of anxiety sensitive to benzodiazepines**
- **Are active in situation involving unavoidable stressful stimuli or following traumatic stress exposure**
- **Show anti-CRF activity**

Do NK_2 receptor antagonists have antidepressant-like properties ?

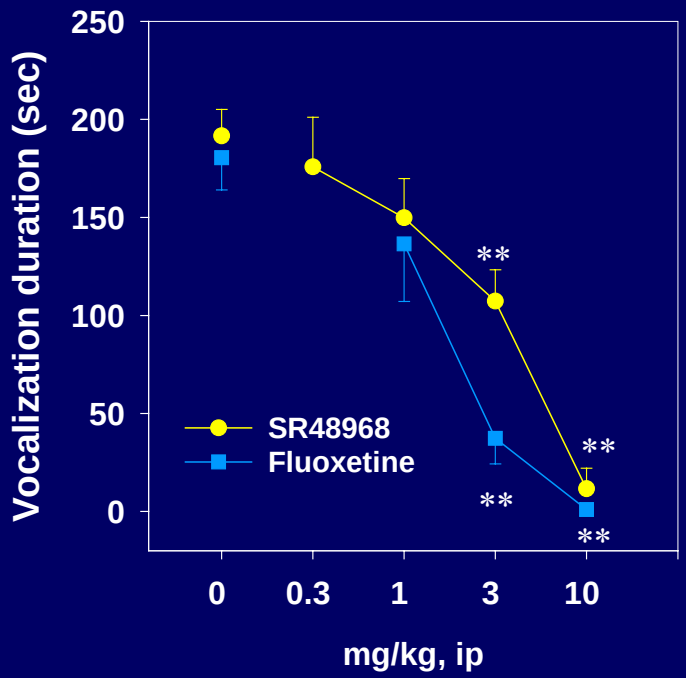
Evidence from behavioral and neurochemical models of depression in rodents

Effects of a selective NK_2 receptor antagonist in two screening models of depression

Forced-swimming test



Maternal separation-induced distress call in guinea-pig pups



Steinberg et al.

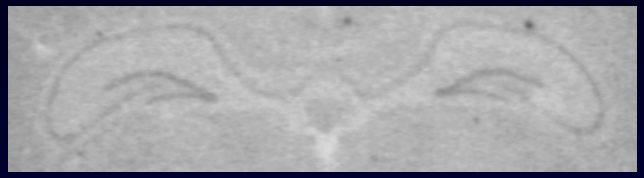
Antidepressants and CREB expression

- **Studies in rodents have implicated the postreceptor components of the cAMP second messenger cascade in the action of different classes of antidepressants**

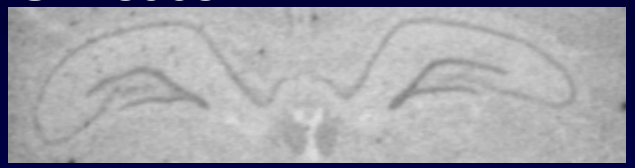
- **Chronic treatment with these drugs upregulated the cAMP system at several levels, including expression of the cAMP response-element binding protein (CREB) in the cerebral cortex and hippocampus**

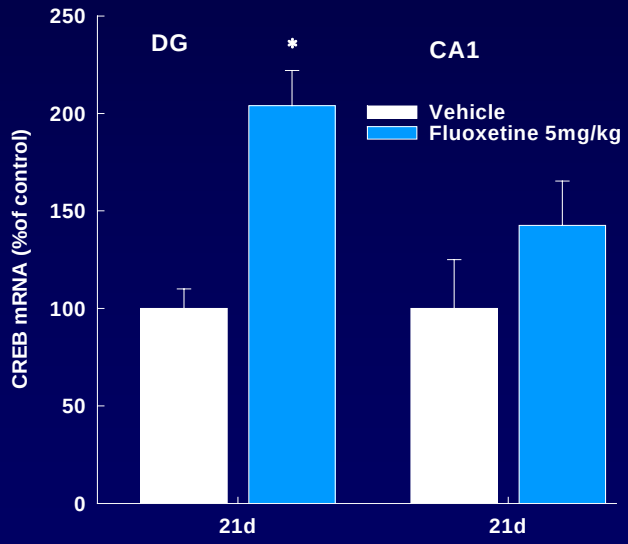
Effects of a selective NK_2 receptor antagonist on CREB mRNA expression in rats

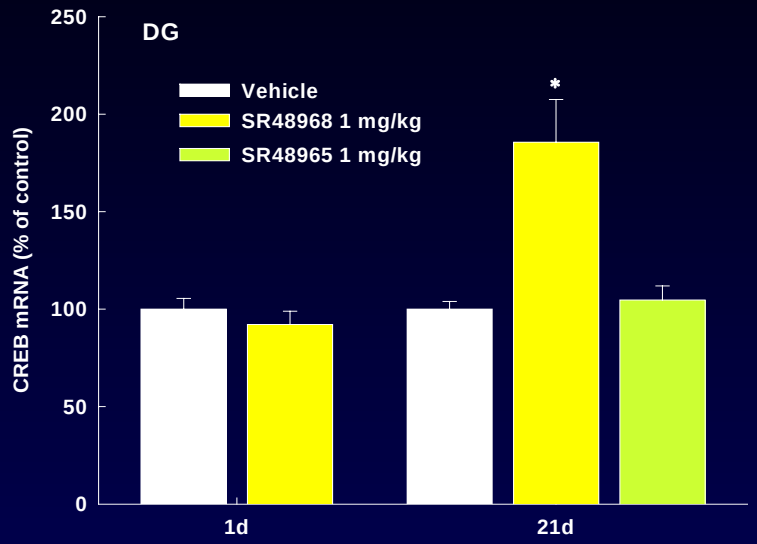
vehicle

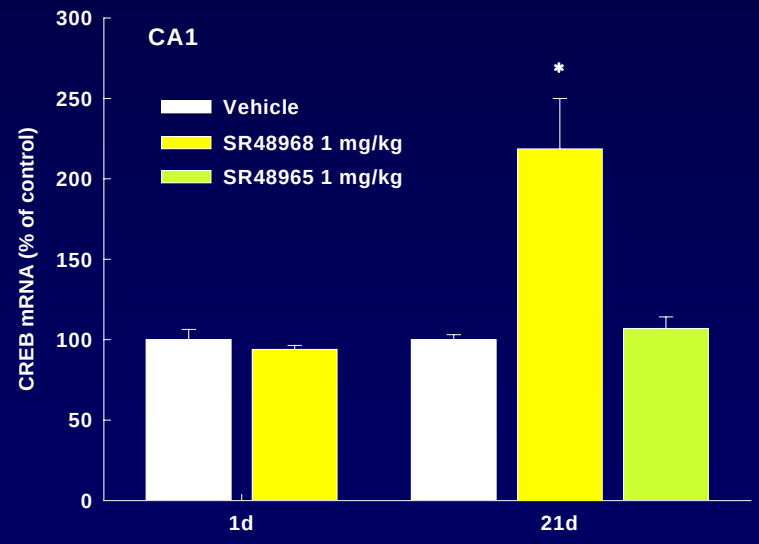


SR48968









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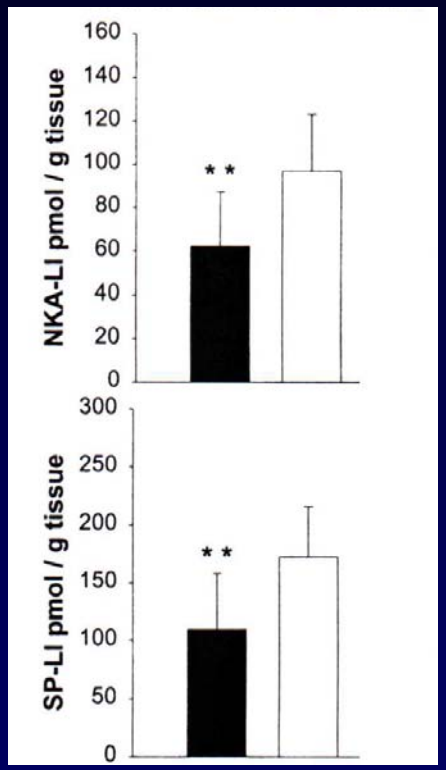
SR48968 in models of depression

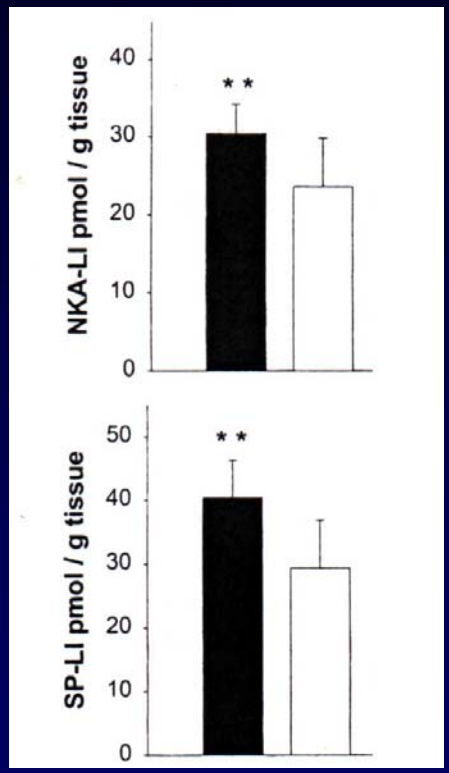
- **Shows good activity in two behavioral models**
- **Sustained blockade of NK_2 receptors leads to an upregulation of the expression of CREB mRNA in the hippocampus, as do antidepressants**

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

STRIATUM



FRONTAL CORTEX

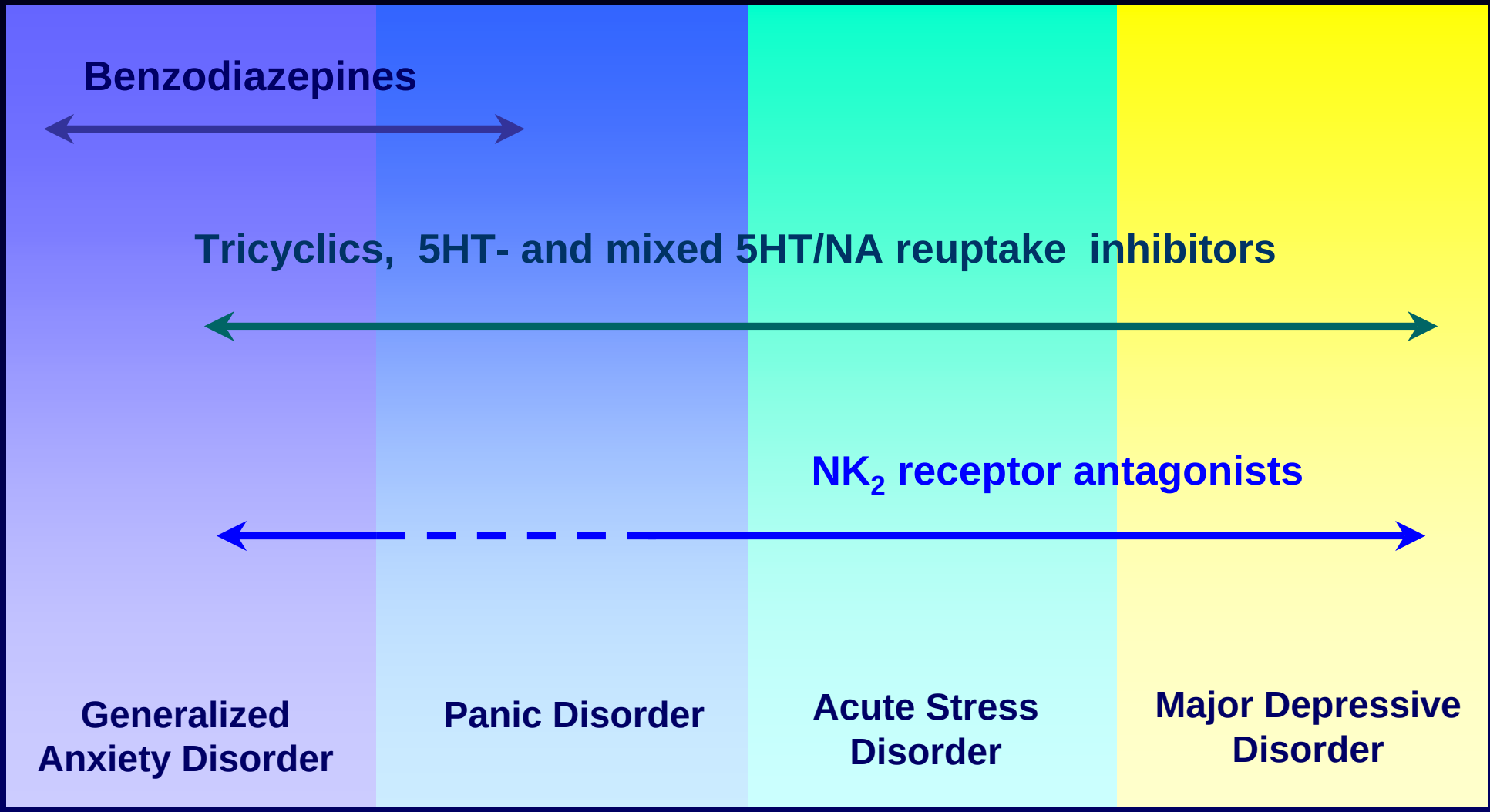


Husum et al. Neuropharmacology 24 : 183-91, 2001

OVERALL SUMMARY

- Studies using classical anxiety models yielded inconsistent data with NK_2 antagonists
- Unlike benzodiazepines, NK_2 antagonists were active in situations involving traumatic stress or unavoidable contact with threatful stimuli
- The NK_2 antagonist SR48968 showed clear antidepressant-like activity

Expected clinical spectrum of therapeutic activity of NK_2 antagonists in anxiety/depressive disorders



Acknowledgements

- **Pharmacology**
  - Calassi R.
  - Jung M.
  - Maruani J.
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  - Simiand J.
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  - Bensaid N.
  - Chardenot P.
  - Oury-Donat F.
- **Chemistry**
  - Emonds-Alt X.
  - Proietto V.
  - Van Broeck D.
- **Electrophysiological studies**
  - Gueudet C.
- **Anatomical studies**
  - Alonso R.
  - Jung M.
- **Neurochemical studies**
  - Bert l.
  - Desvignes C.
  - Bougault I.
  - Leonetti M.
  - Mons G.
  - Rodier D.
  - Souilhac J.
  - Steinberg R.