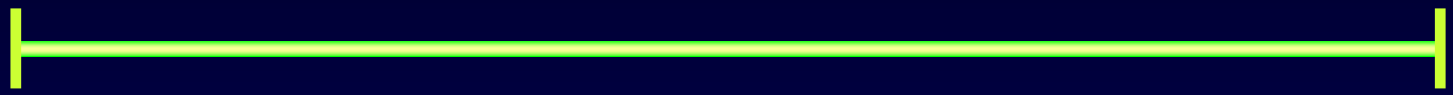
BRAIN NEUROKININ-2 RECEPTORS AS POTENTIAL TARGETS FOR ANXIOLYTICS AND ANTIDEPRESSANTS



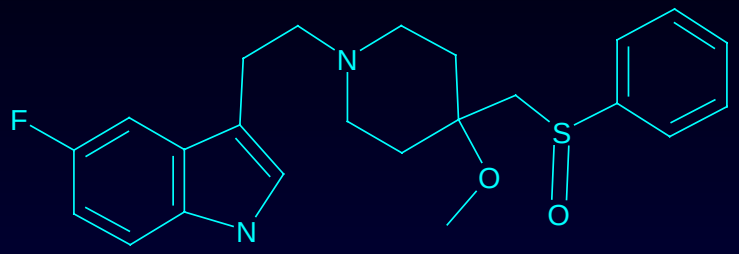
« No apparent expression of SKR (NK_2) mRNA in the CNS »

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

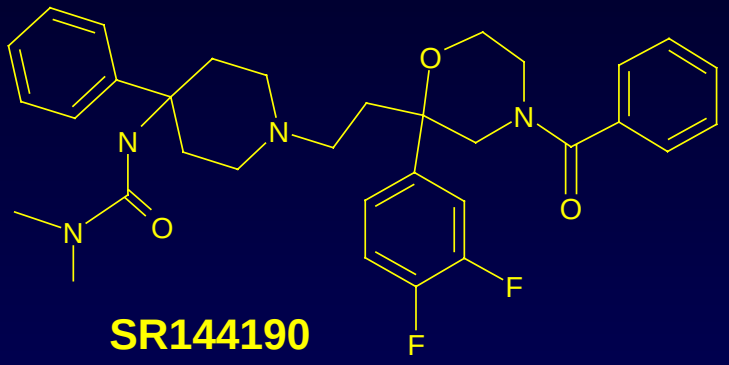
First clinical trial (Phase IIa) with a selective NK_2 antagonist in major depressive disorder

Selective and potent non-peptide NK_2 receptor antagonists

SR48968



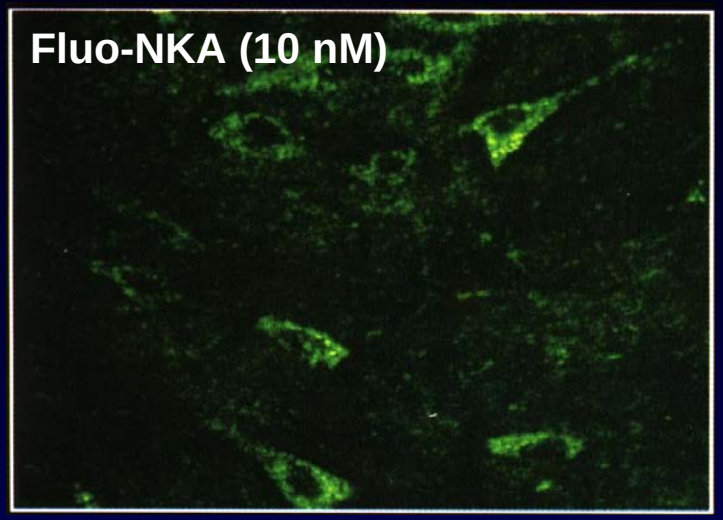
GR159897

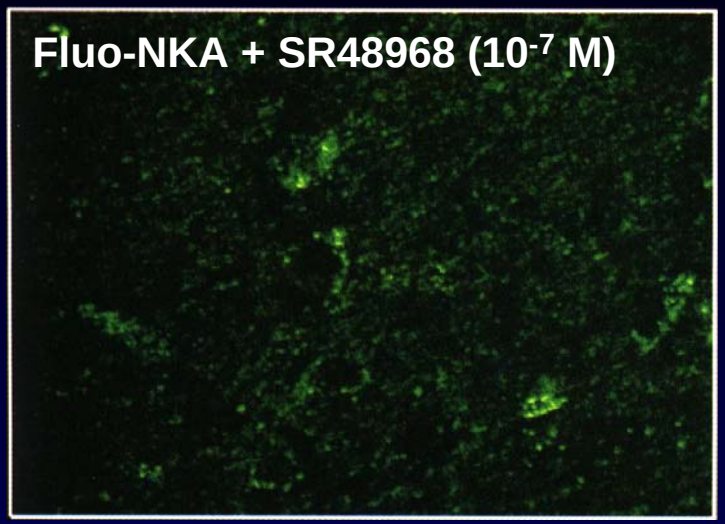


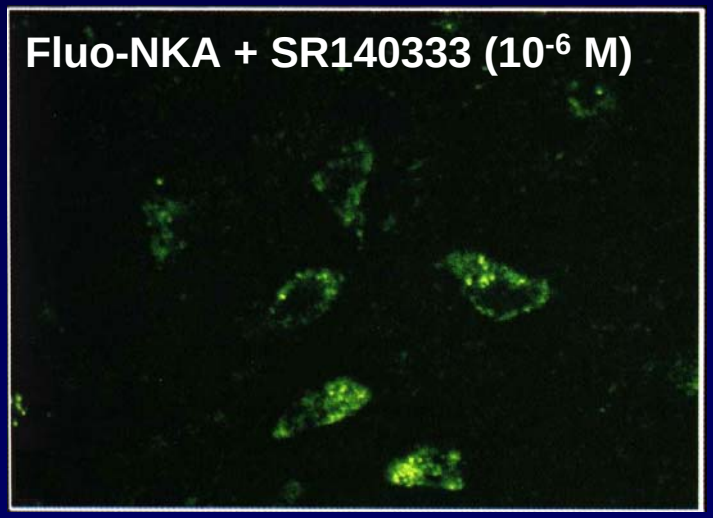
SR144190

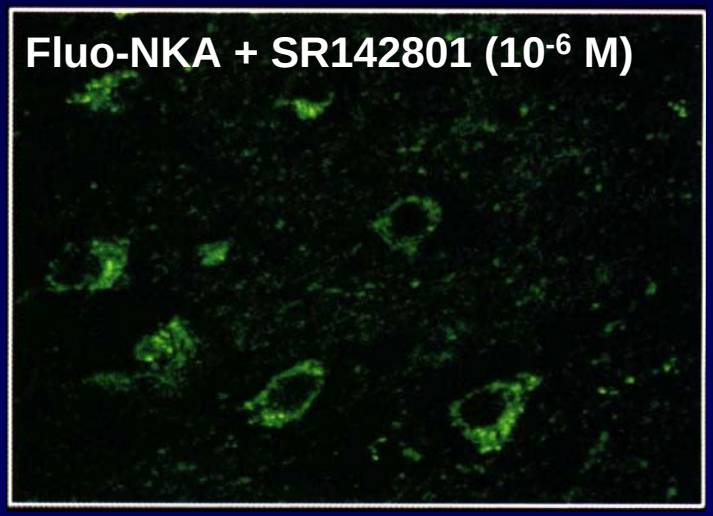
	hNK$_2$-CHOpKi	pA$_2$	
GR159897	9.5	8.72	Beresford et al. (1995)
SR48968	9.9	10.3	Emonds-Alt et al. (1992)
SR144190		10.1	Emonds-Alt et al. (1997)

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



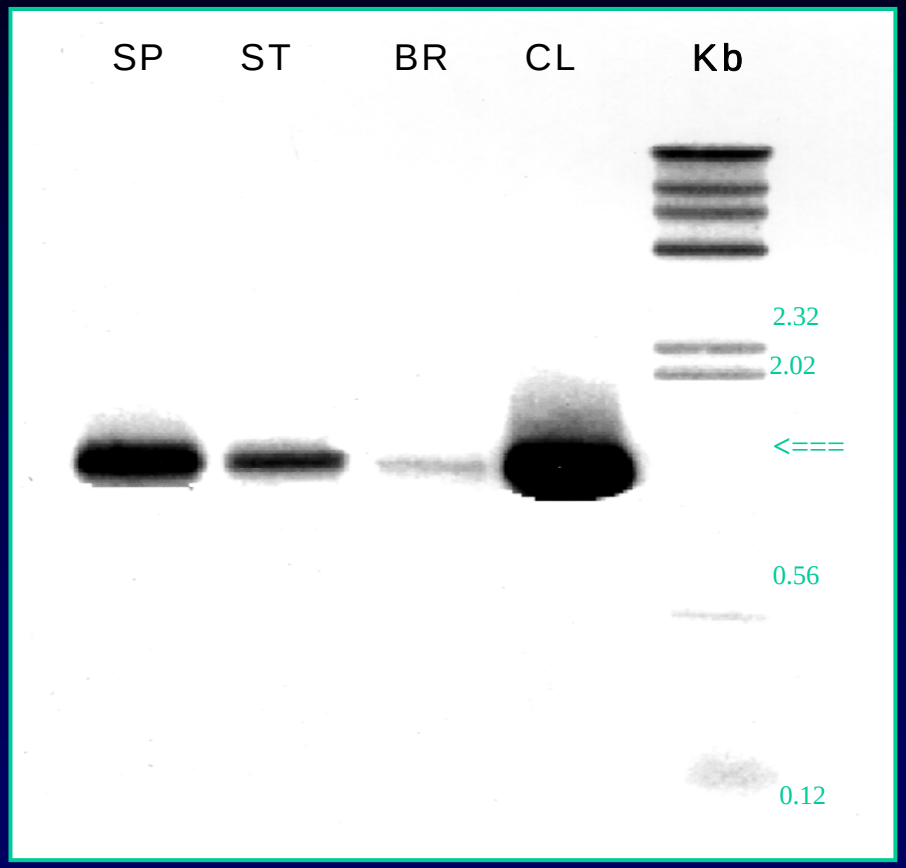






Steinberg et al. Eur. J. Neurosci. 10 : 2337-45, 1998

Analysis by RT-PCR of NK_2 receptor expression in various rat tissues including septum (SP), striatum (ST), whole brain (BR) and colon (CL)



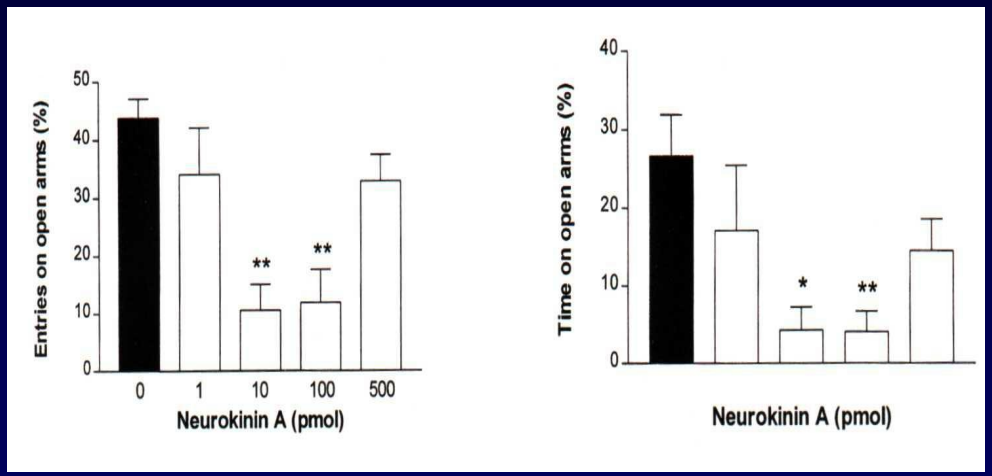
Steinberg et al., Eur. J. Neurosci. 10 : 2337-45, 1998

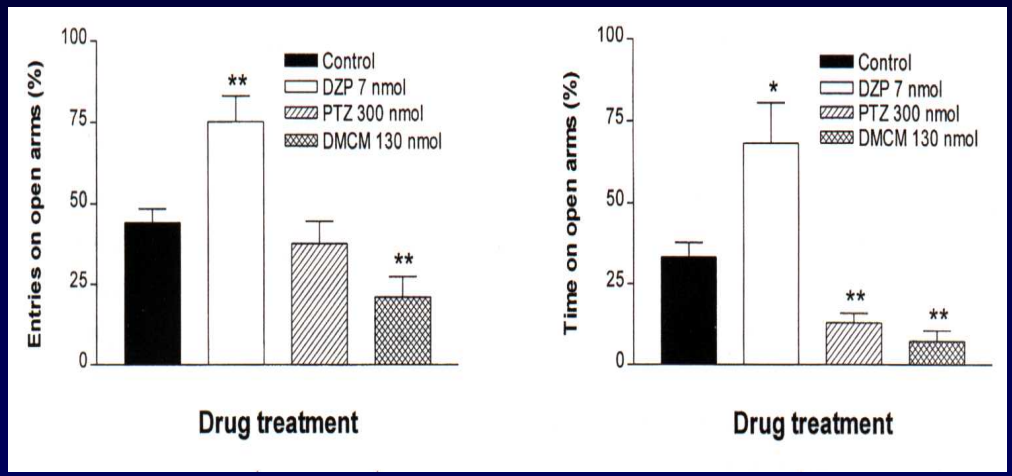
Structures and properties of rat tachykinin receptors

	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?

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

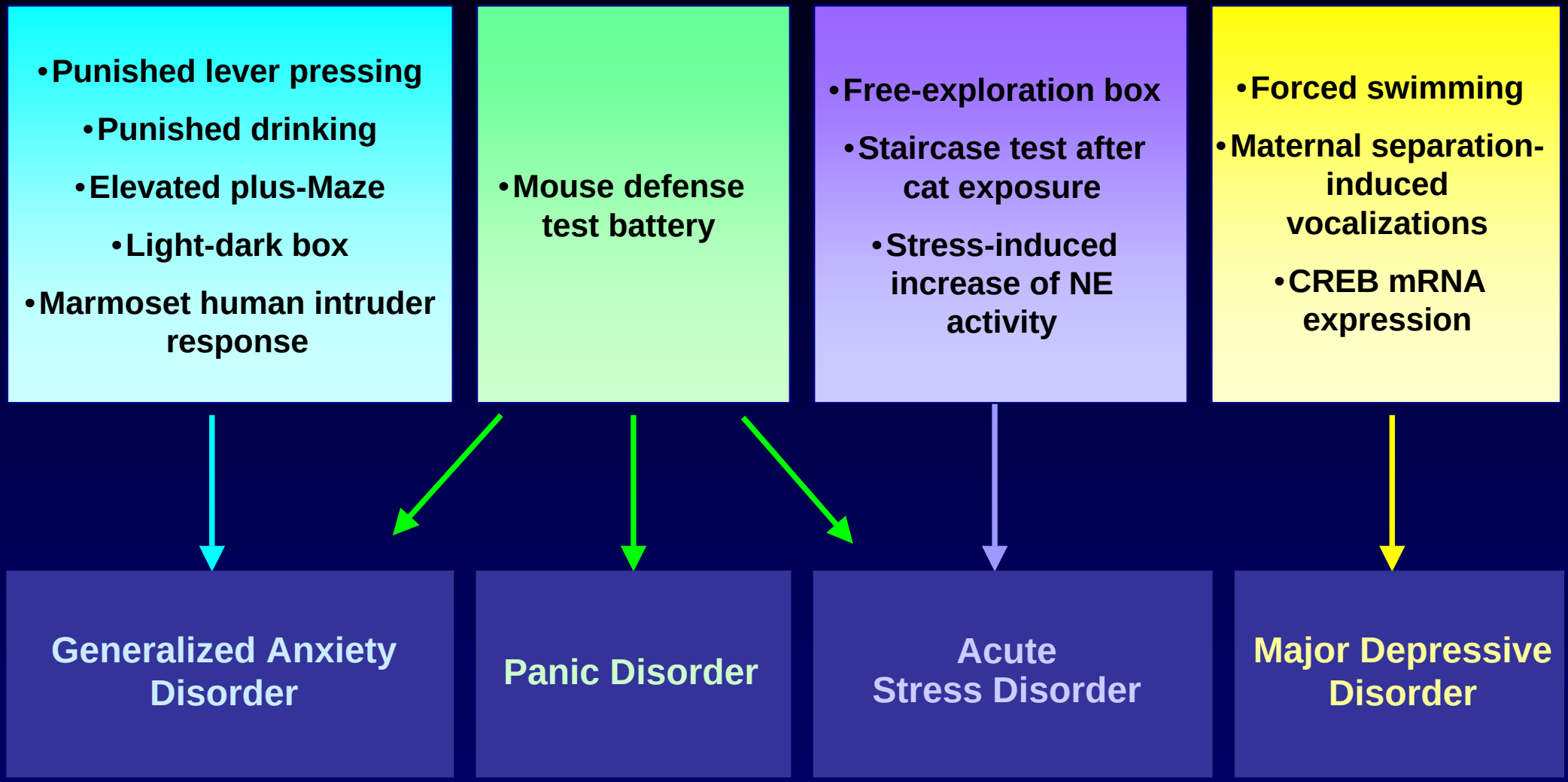




Teixeira et al. Eur. J. Pharmacol. 311 : 7-14, 1996

Do selective NK_2 receptor antagonists modulate emotional behaviors ?

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

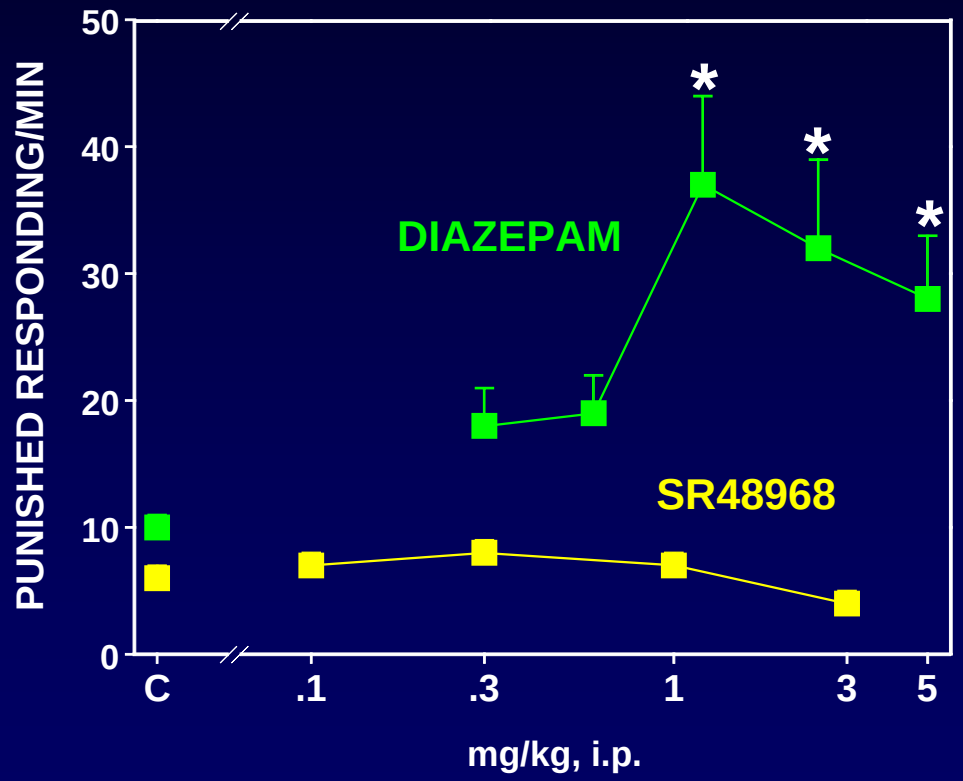


Do NK_2 receptor antagonists have anxiolytic-like properties ?

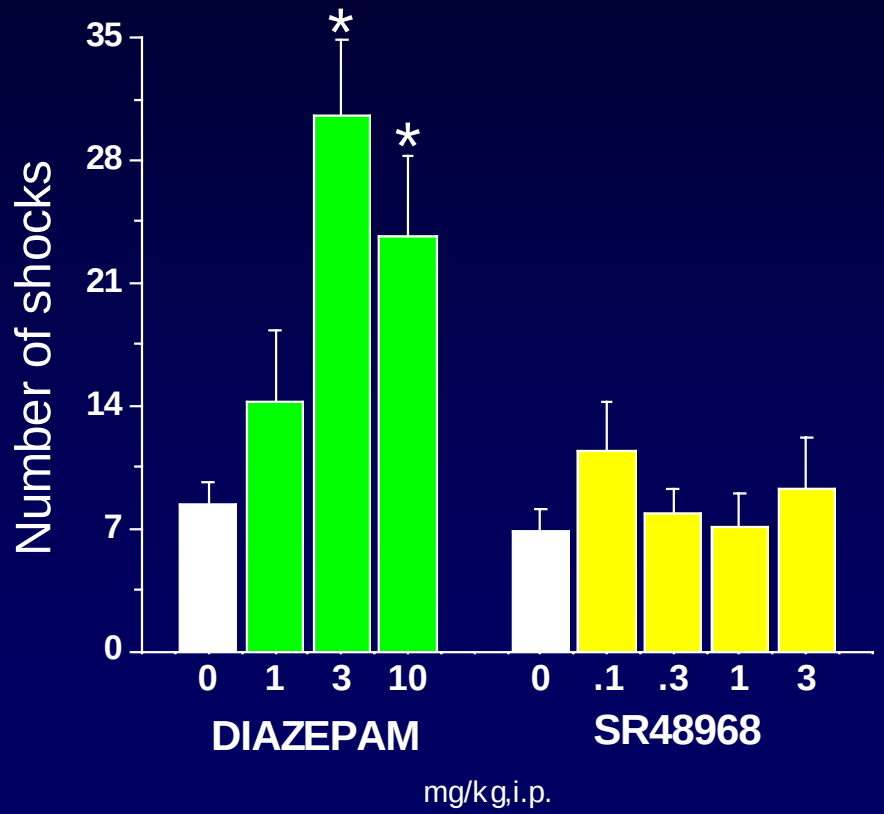
Evidence from behavioral and neurochemical models of anxiety/stress disorders

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

Punished lever pressing test

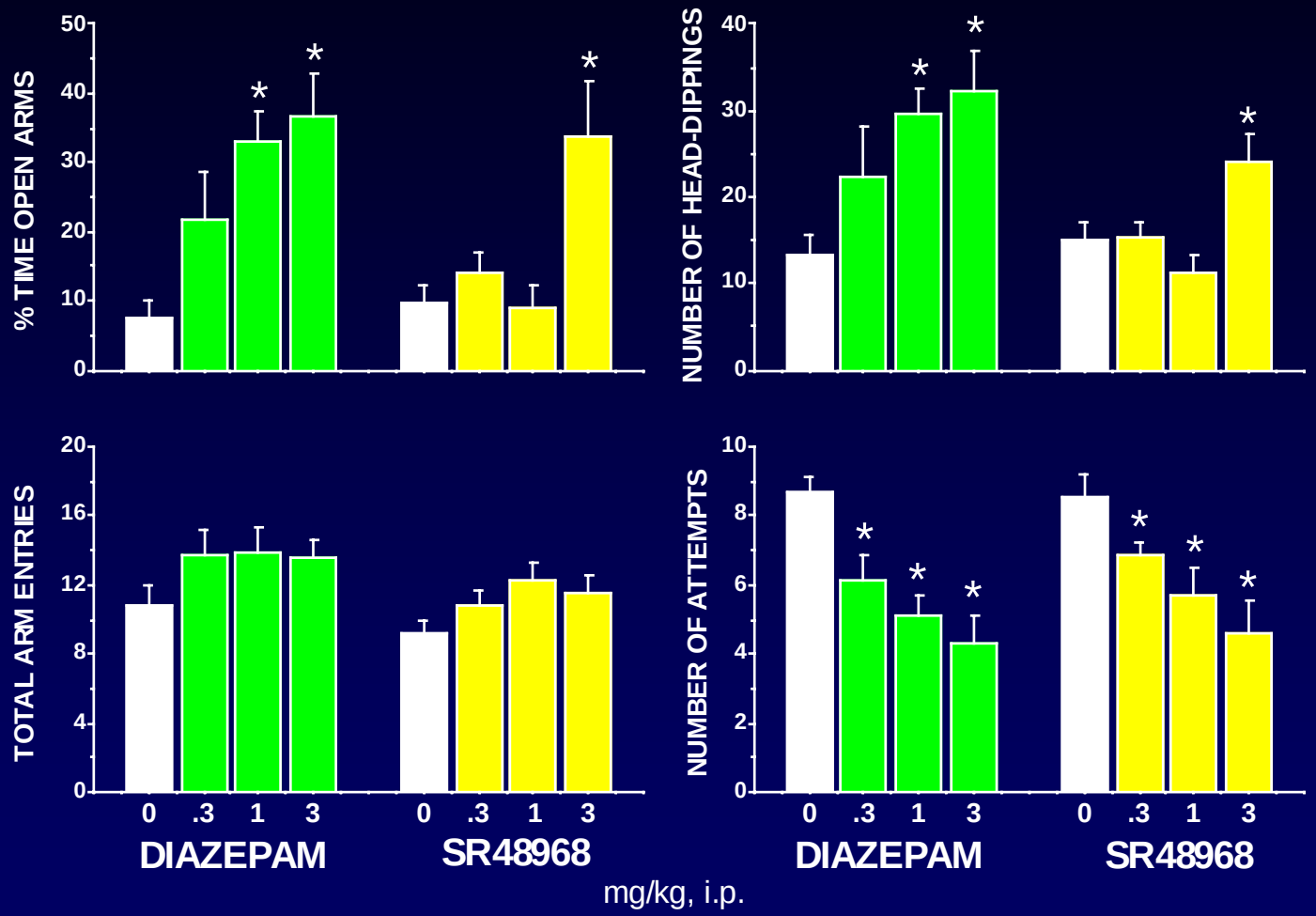


Punished drinking test



Griebel et al., Psychopharmacology (in press)

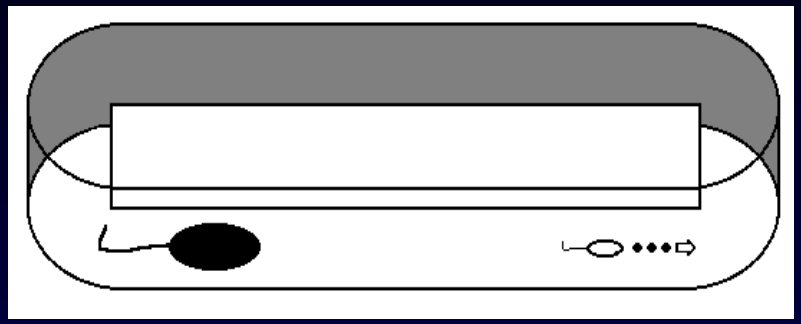
Effects of a selective NK_2 receptor antagonist in the elevated plus-maze test in rats



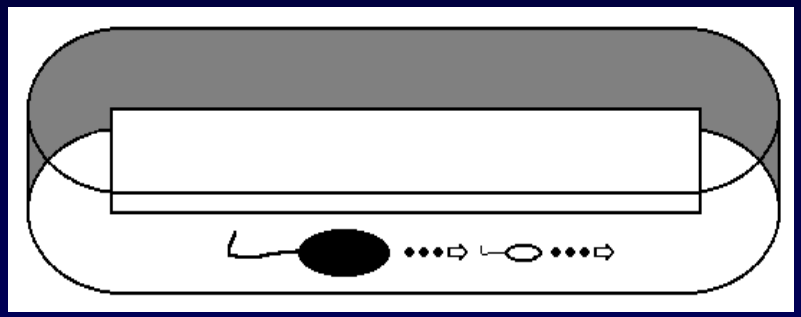
Griebel et al., Psychopharmacology (in press)

The mouse defense test battery

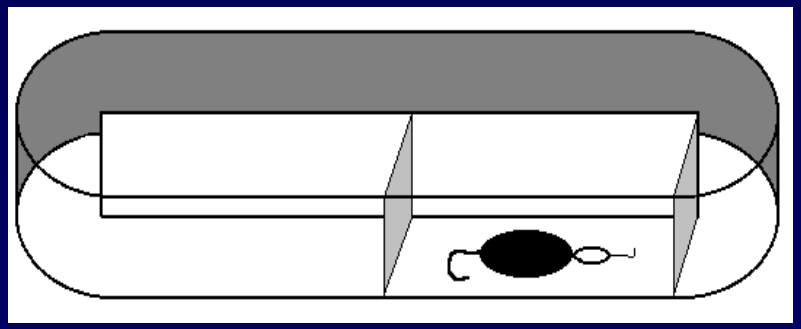
FLIGHT



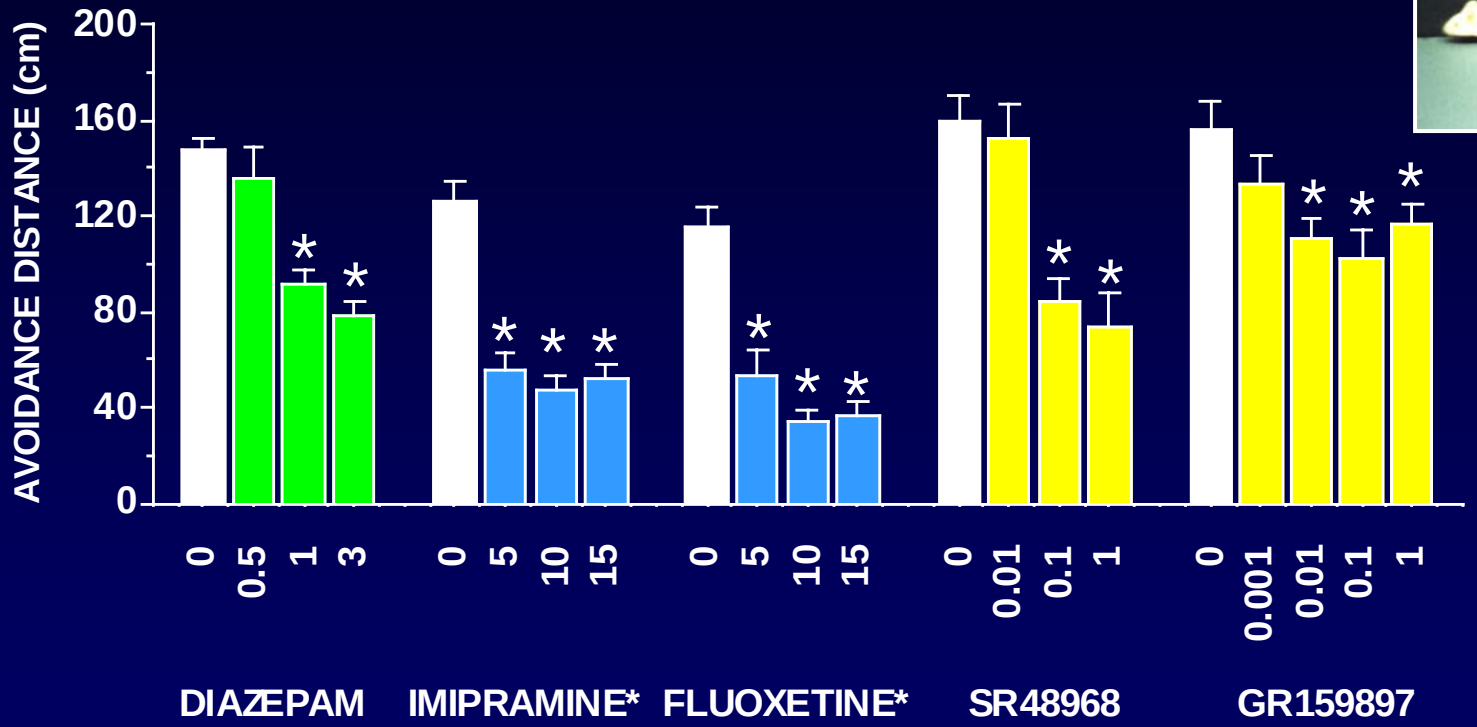
RISK ASSESSMENT



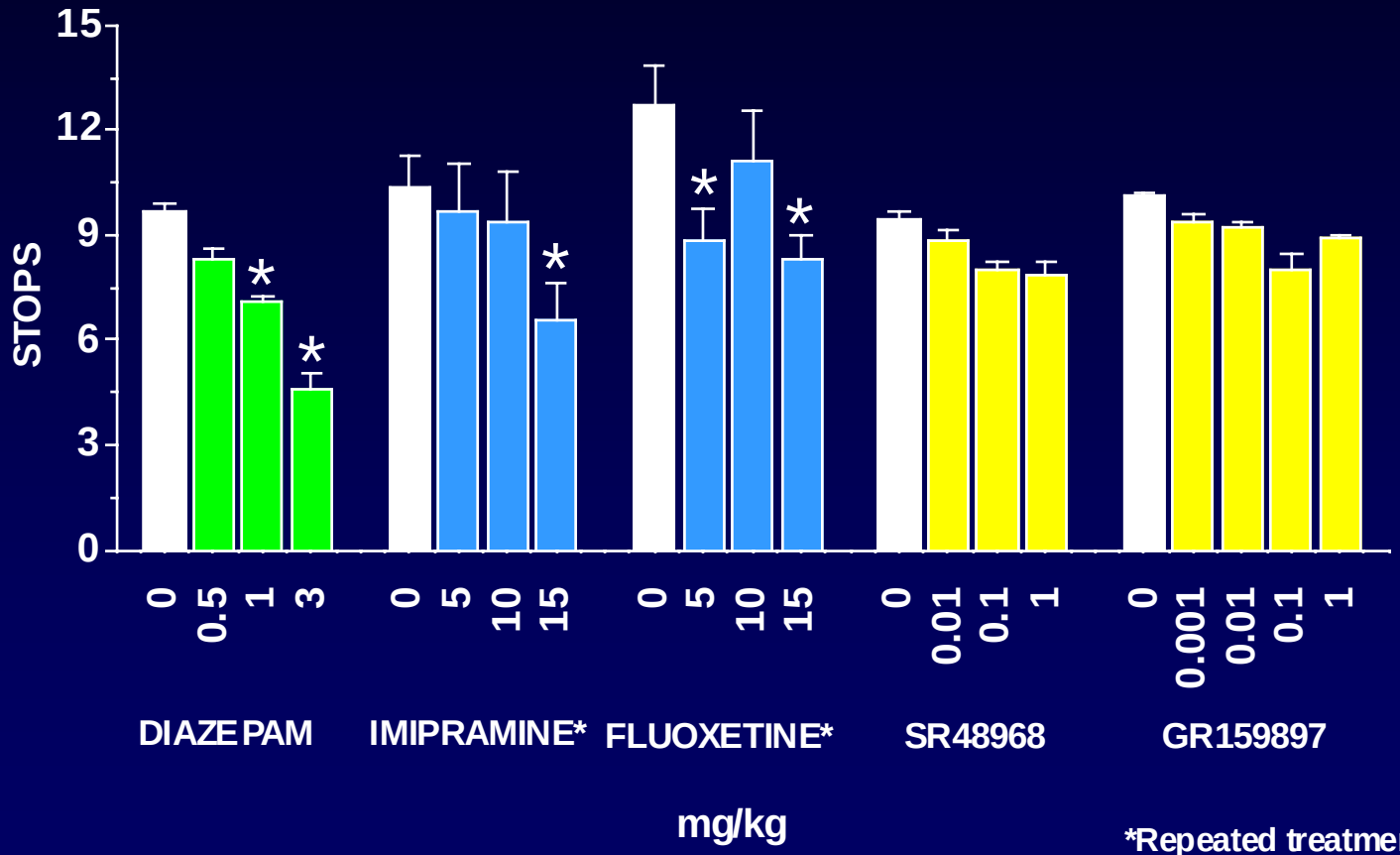
DEFENSIVE AGGRESSION



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

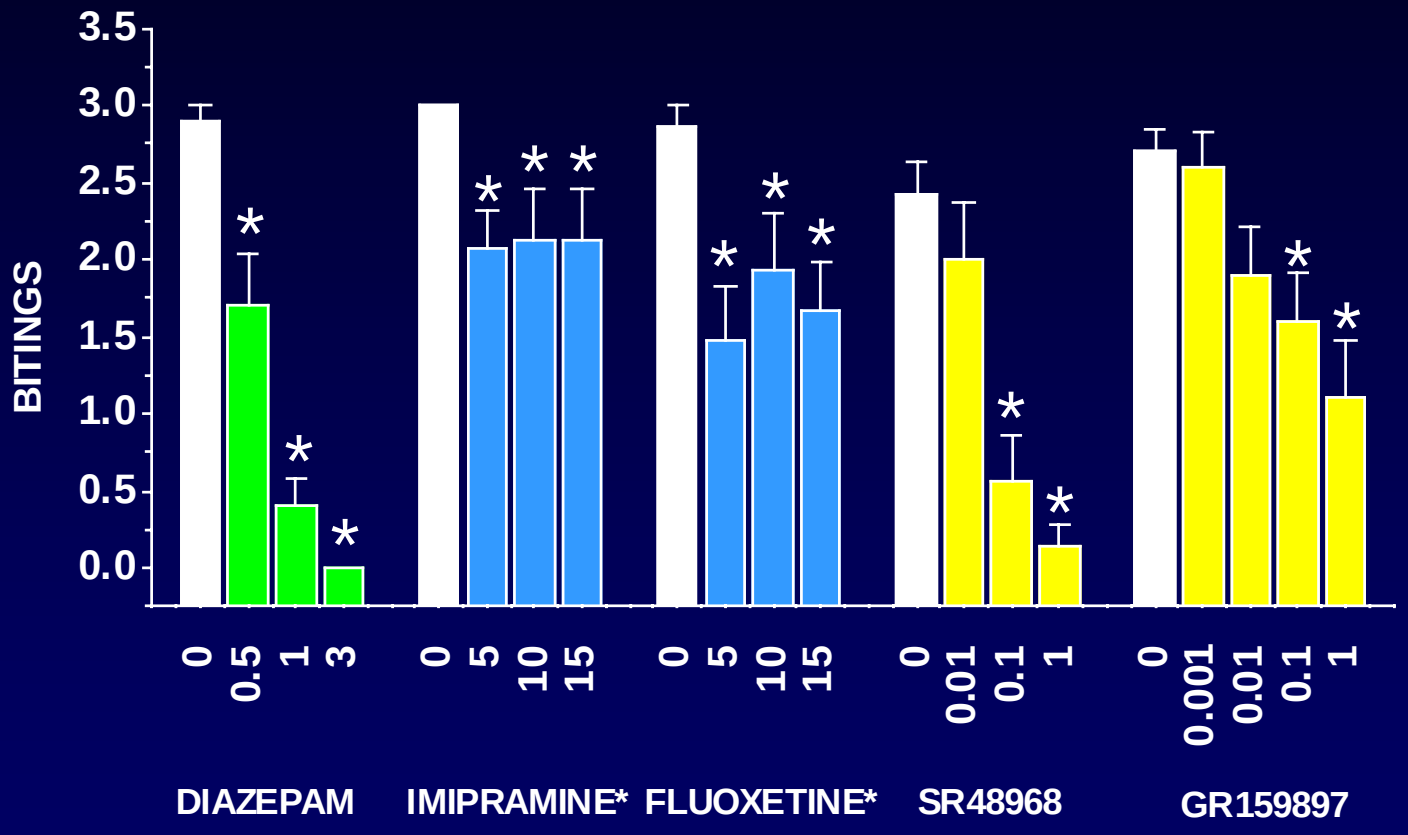


Effects of selective NK_2 receptor antagonists on risk assessment behavior in the mouse defense test battery



*Repeated treatment

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



*Repeated treatment

Investigation of the behavior of rodents following cat exposure

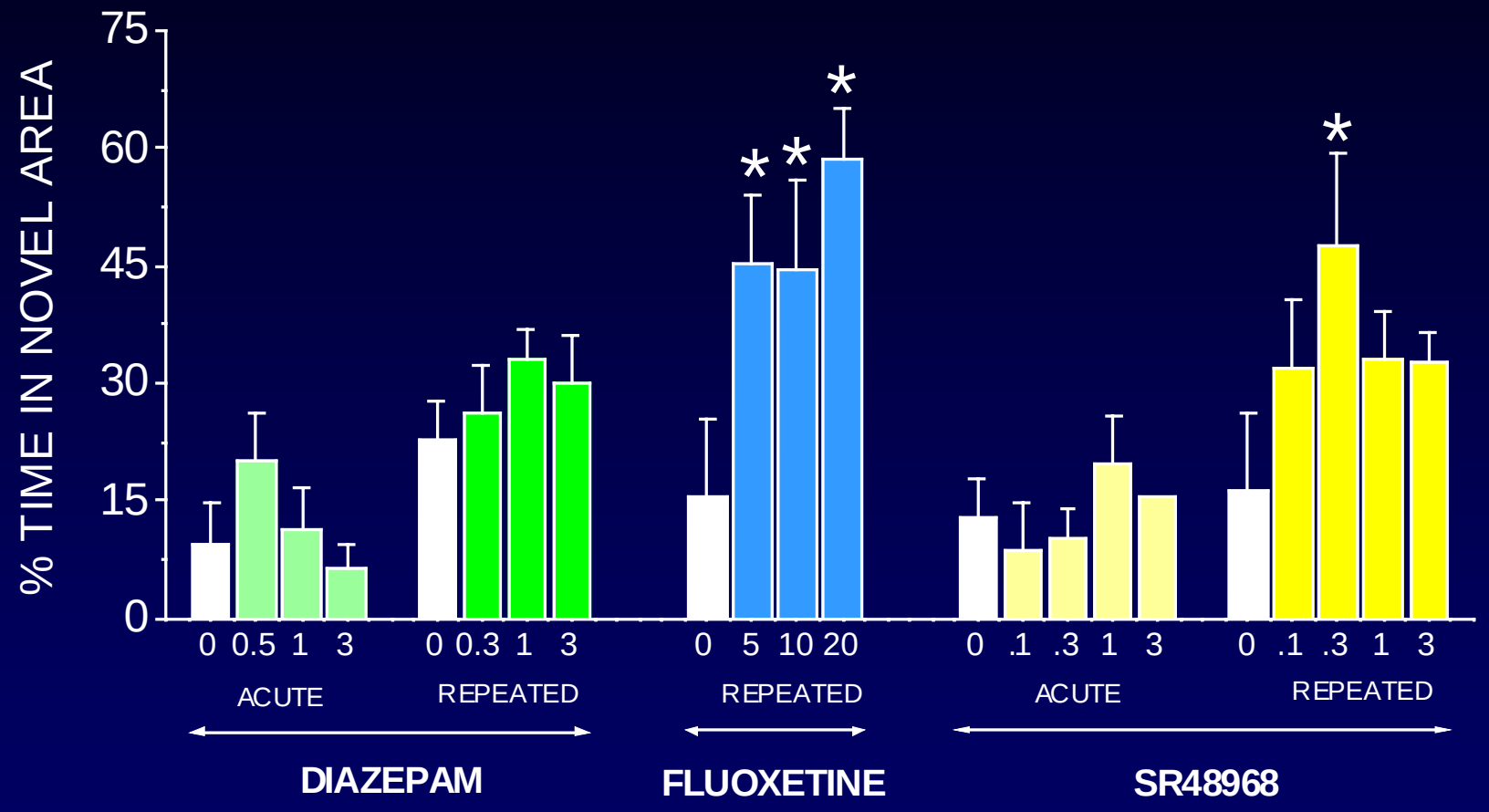
Cat exposure (5-10 min)

60 min

Free exploration test

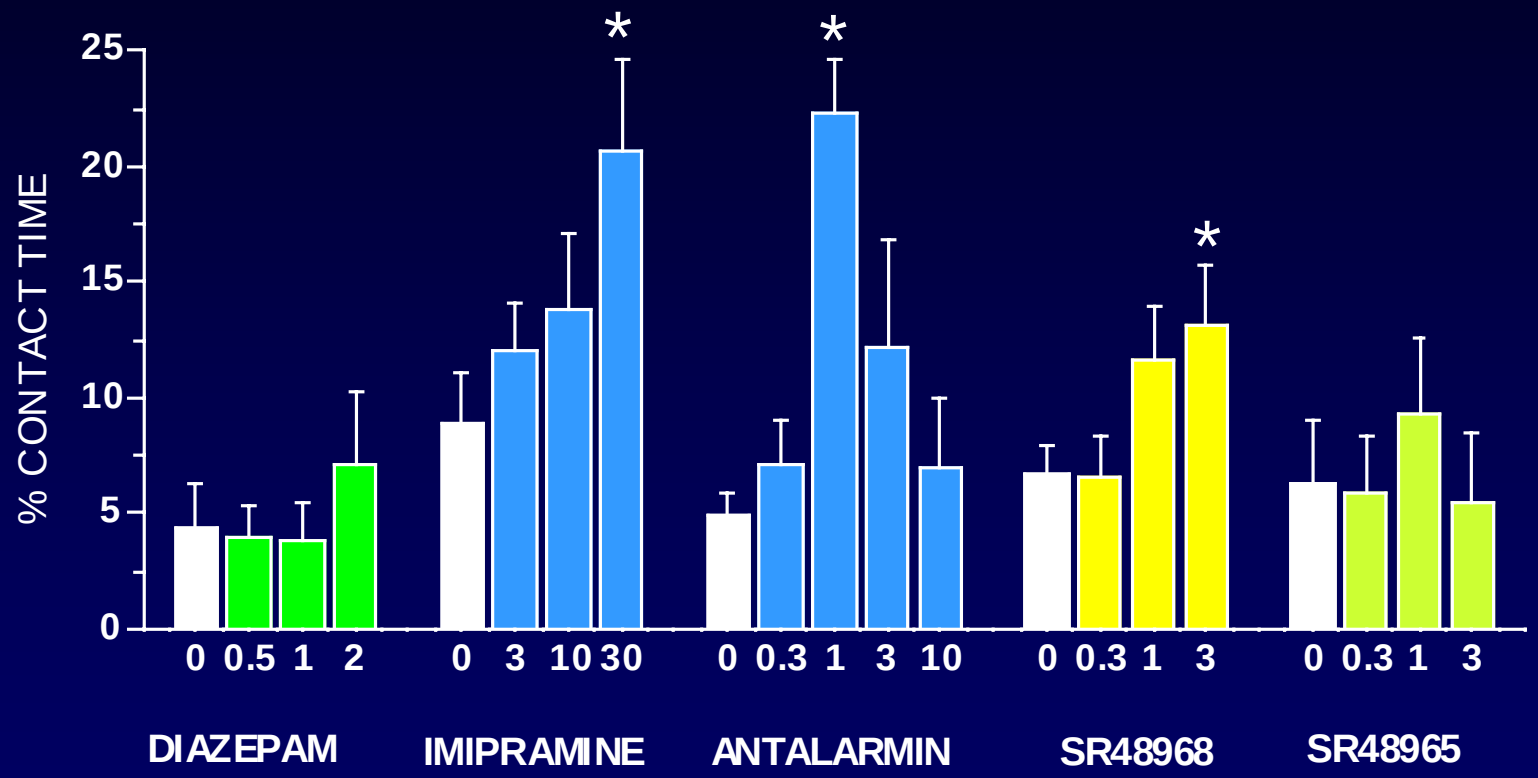
Staircase test

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



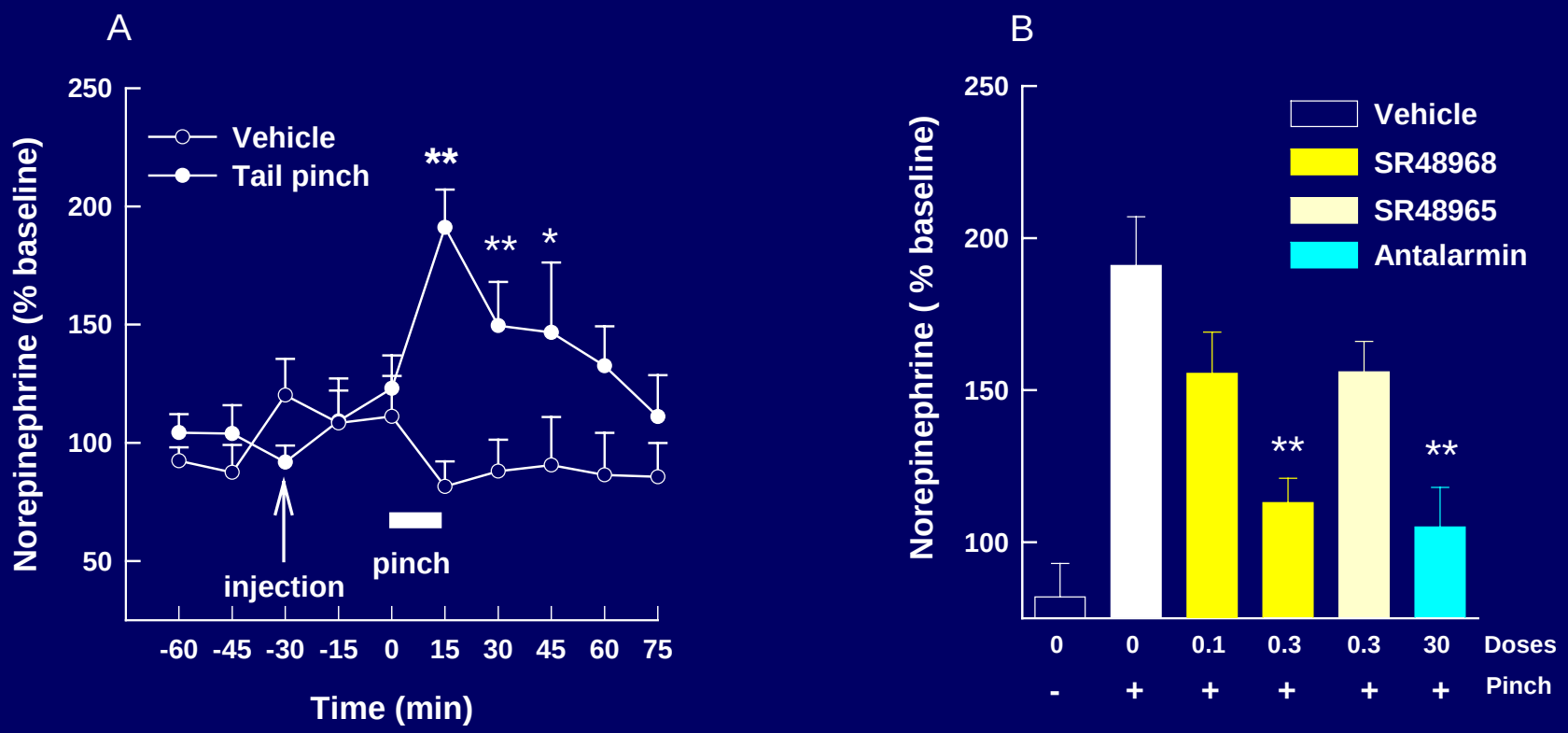
Griebel et al., Psychopharmacology (in press)

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



Griebel et al., Psychopharmacology (in press)

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., J. Pharmacol. Exp. Ther 299, 2001 (in press)

NK_2 antagonists in models of anxiety-related disorders

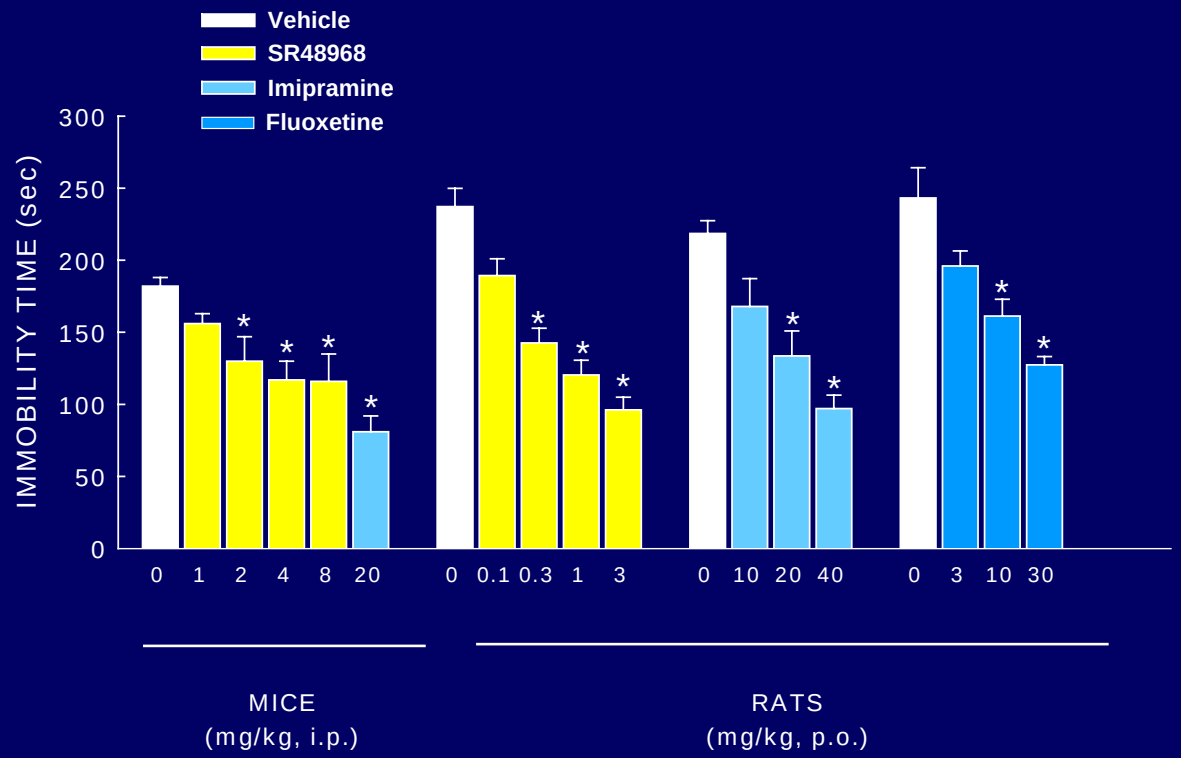
- **Show limited efficacy in models of anxiety sensitive to benzodiazepines**
- **Are active in situation involving unavoidable stressful stimuli or following traumatic stress exposure**

Do NK_2 receptor antagonists have antidepressant-like properties ?

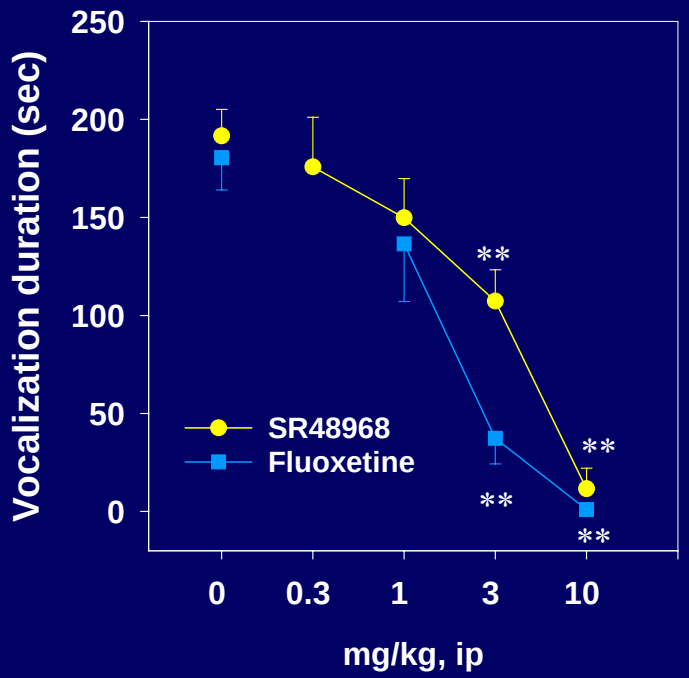
Evidence from behavioral and neurochemical models of depression in rodents

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

Forced-swimming test



Maternal separation-induced distress calls in guinea-pig pups



Steinberg et al., J. Pharmacol. Exp. Ther 299, 2001 (in press)

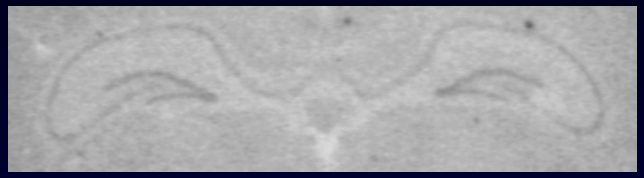
Antidepressants and CREB expression

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

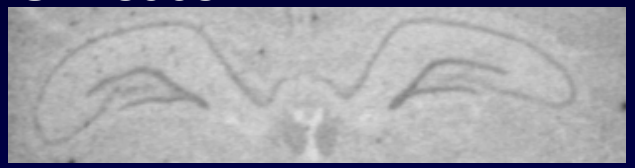
- **Chronic treatment with these drugs upregulated the cAMP system at several levels, including expression of the cAMP response-element binding protein (CREB) in the cerebral cortex and hippocampus**

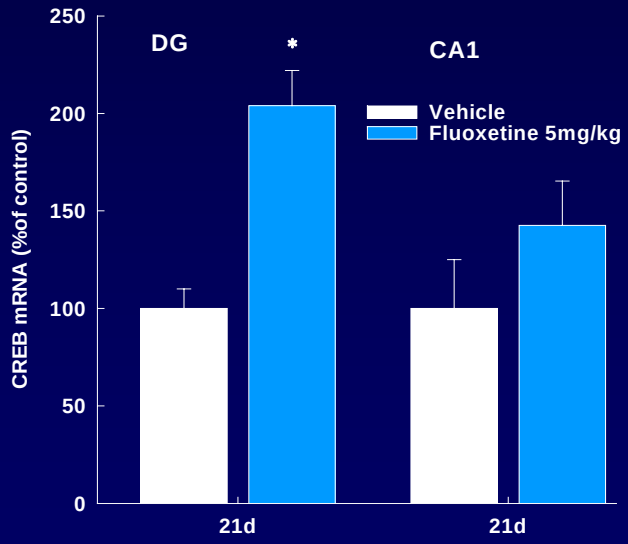
Effects of a selective NK_2 receptor antagonist on CREB mRNA expression in rats

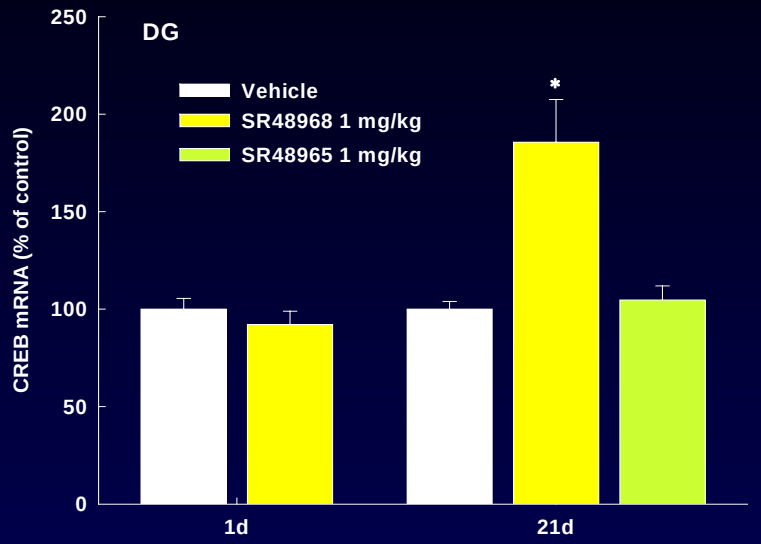
vehicle

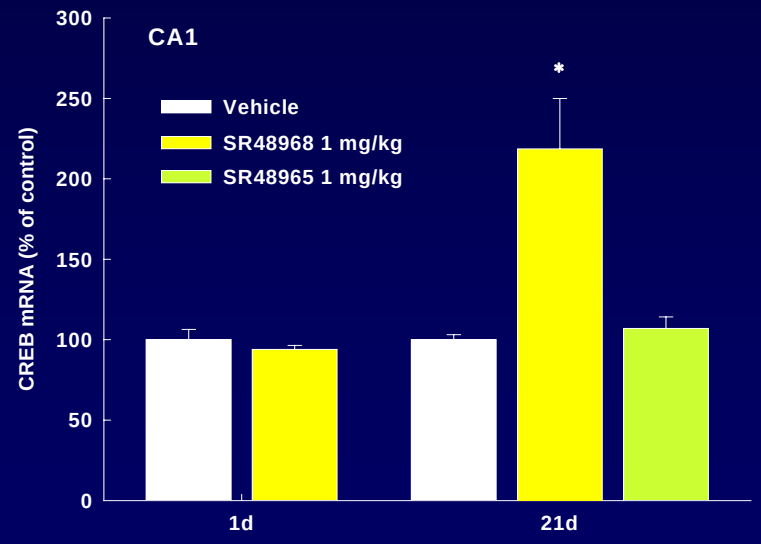


SR48968









Steinberg et al., J. Pharmacol. Exp. Ther 299, 2001 (in press)

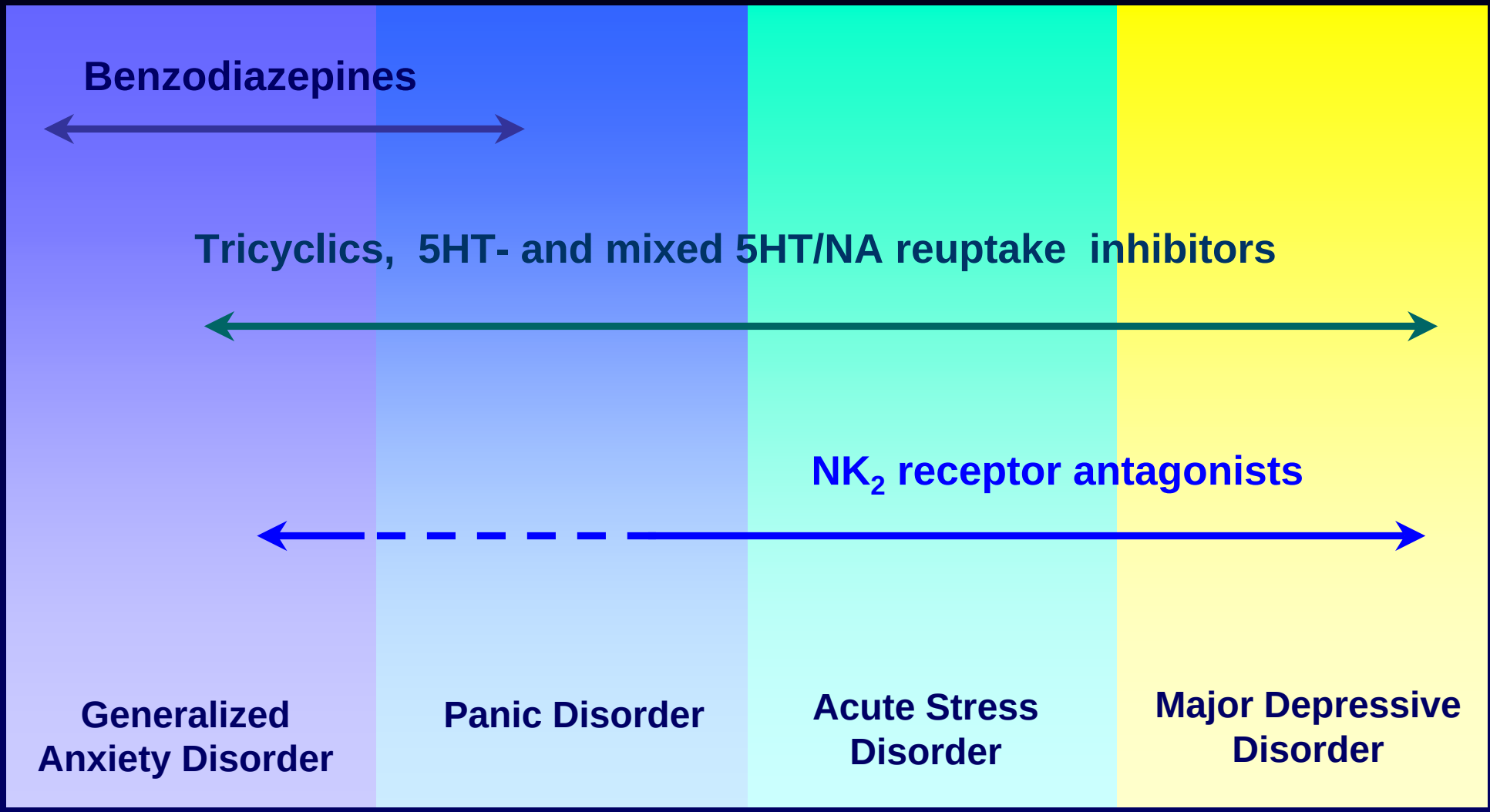
SR48968 in models of depression

- **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**

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 threatening 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.
  - Poncelet M.
  - Simiand J.
- **Molecular studies**
  - 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.