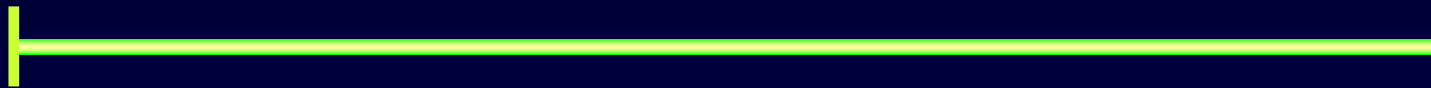


BRAIN NEUROKININ-2 RECEPTORS AS
POTENTIAL TARGETS FOR ANXIOLYTICS
AND ANTIDEPRESSANTS

1990

2000

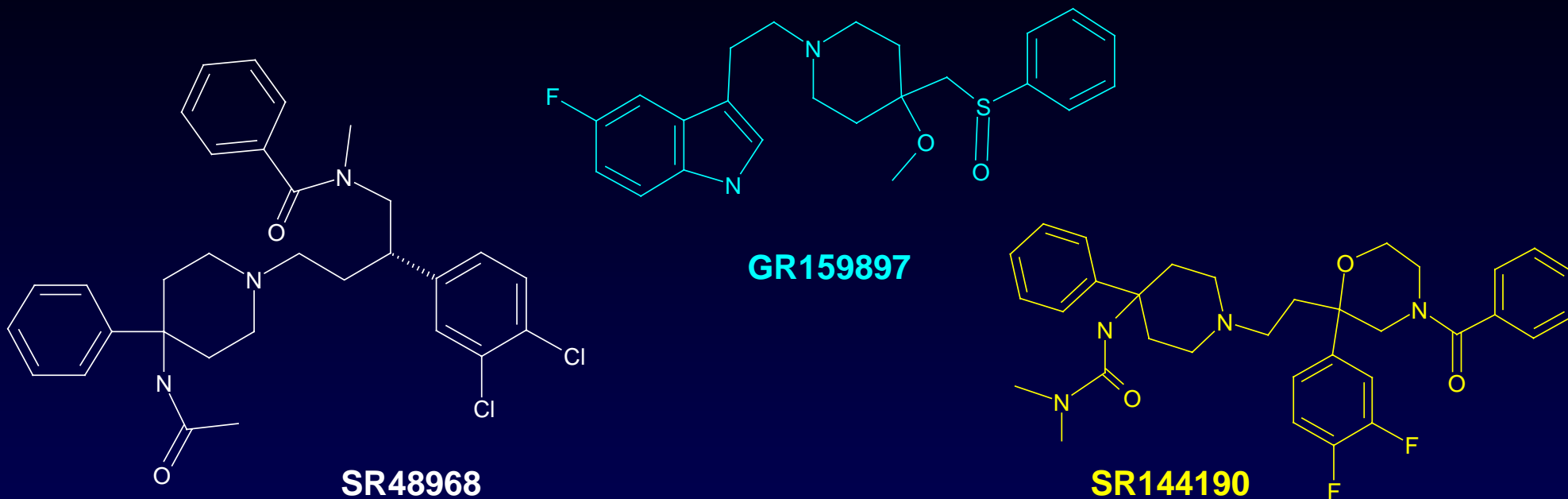


« No apparent
expression of SKR
(NK₂) mRNA in the
CNS »

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

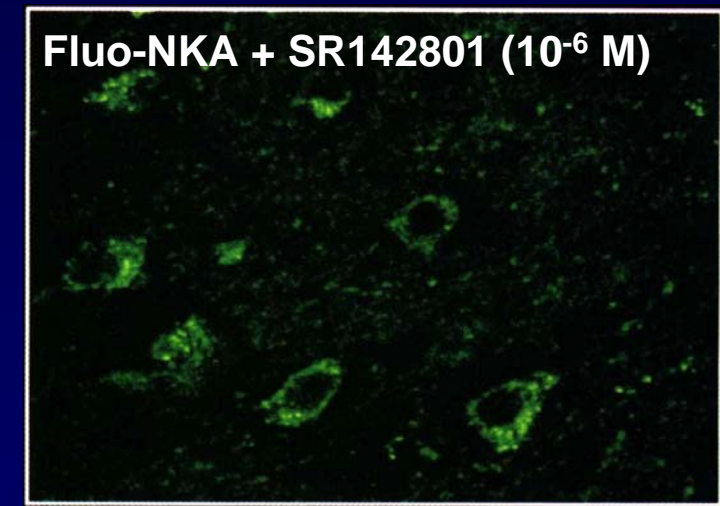
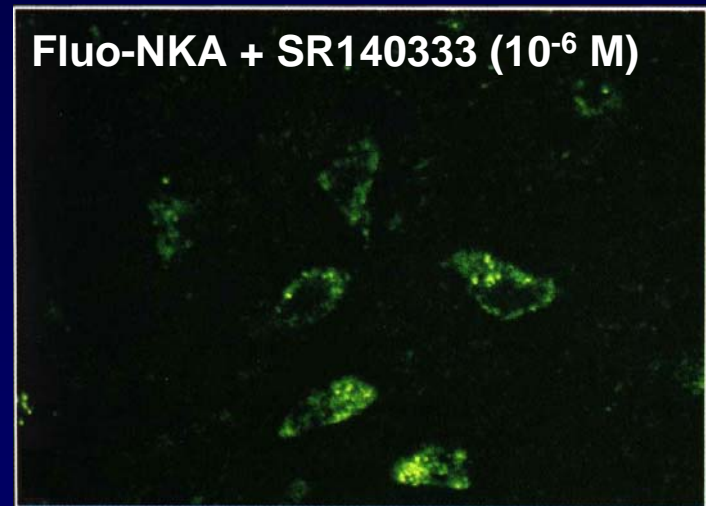
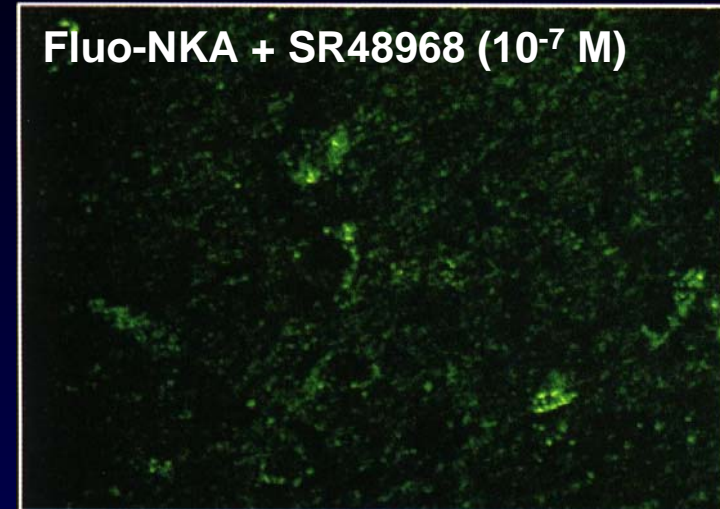
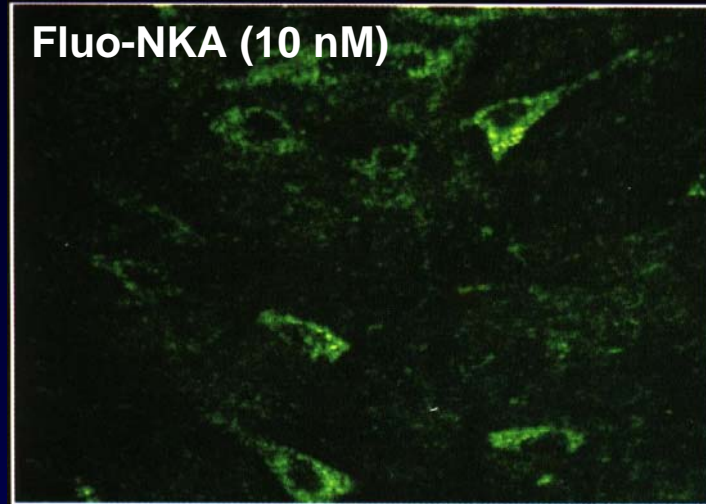
First clinical trial
(Phase IIa) with a
selective NK₂
antagonist in major
depressive disorder

Selective and potent non-peptide NK₂ receptor antagonists

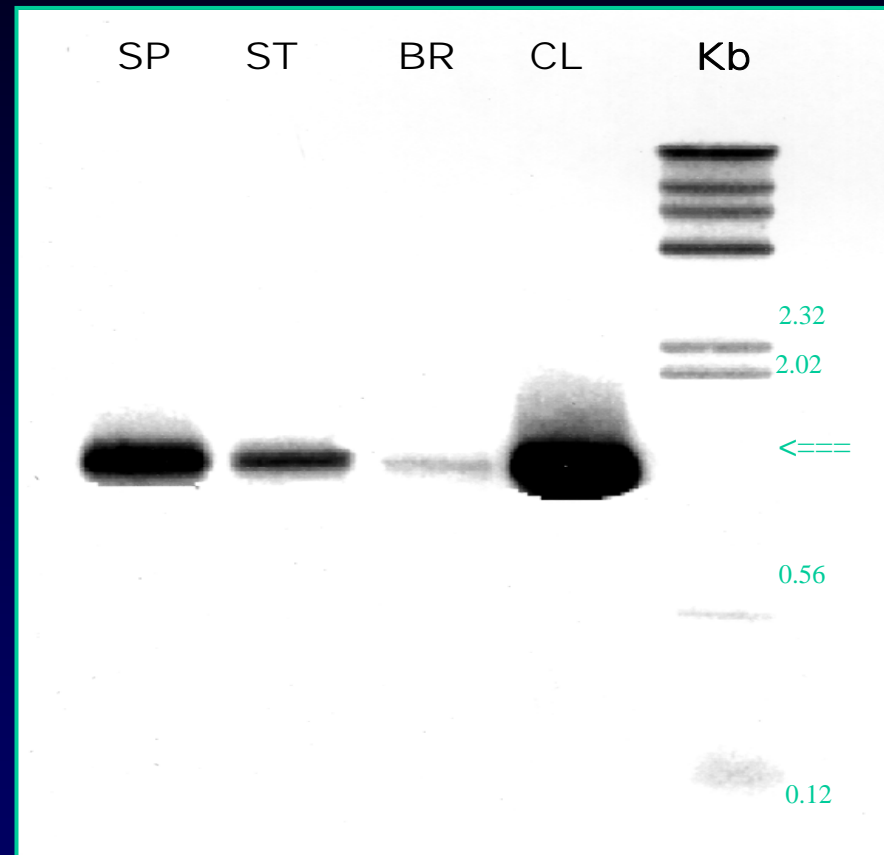


	hNK ₂ -CHO _p Ki	pA ₂	
GR159897	9.5	8.72	Beresford et al. (1995)
SR48968	9.9	10.3	Emonds-Alt et al. (1992)
SR144190		10.1	Emonds-Alt et al. (1997)

Evidence for the presence of 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)



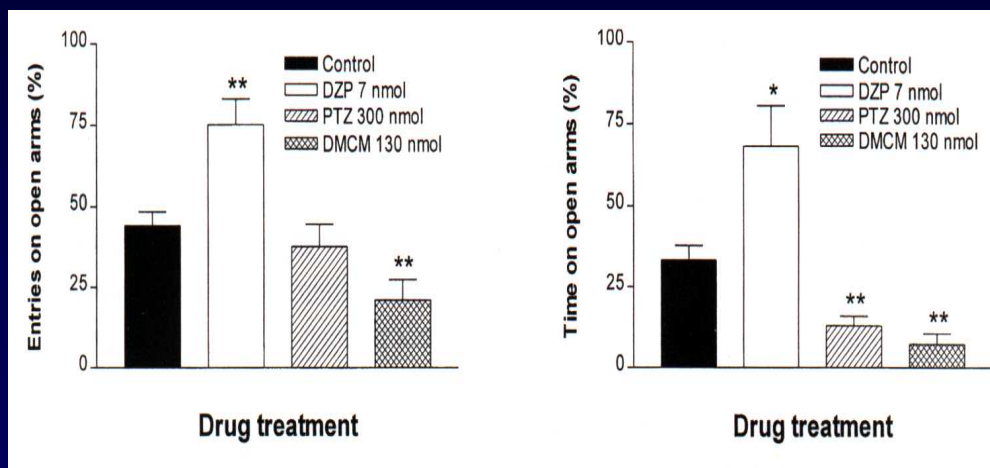
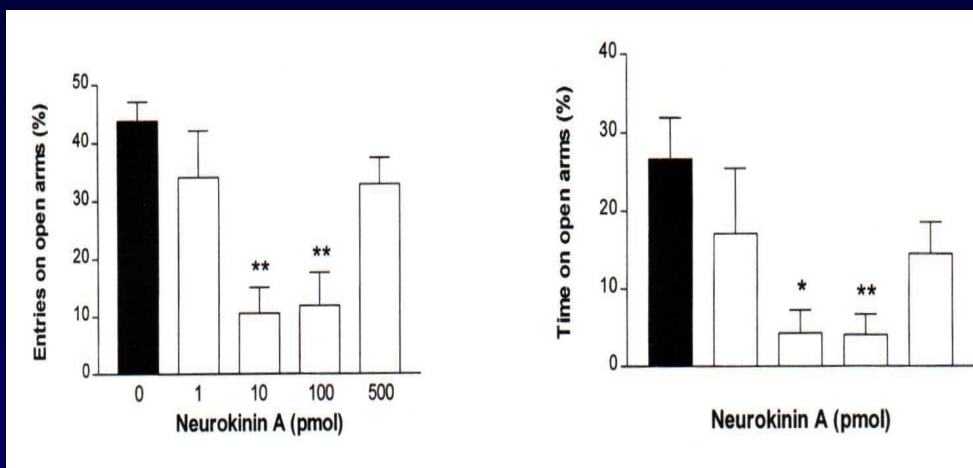
Steinberg et al., *Eur. J. Neurosci.* 10 : 2337-45, 1998

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
NK₂ 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



Do selective NK₂ receptor
antagonists modulate emotional
behaviors ?

Animal models used to investigate the effects of NK₂ 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

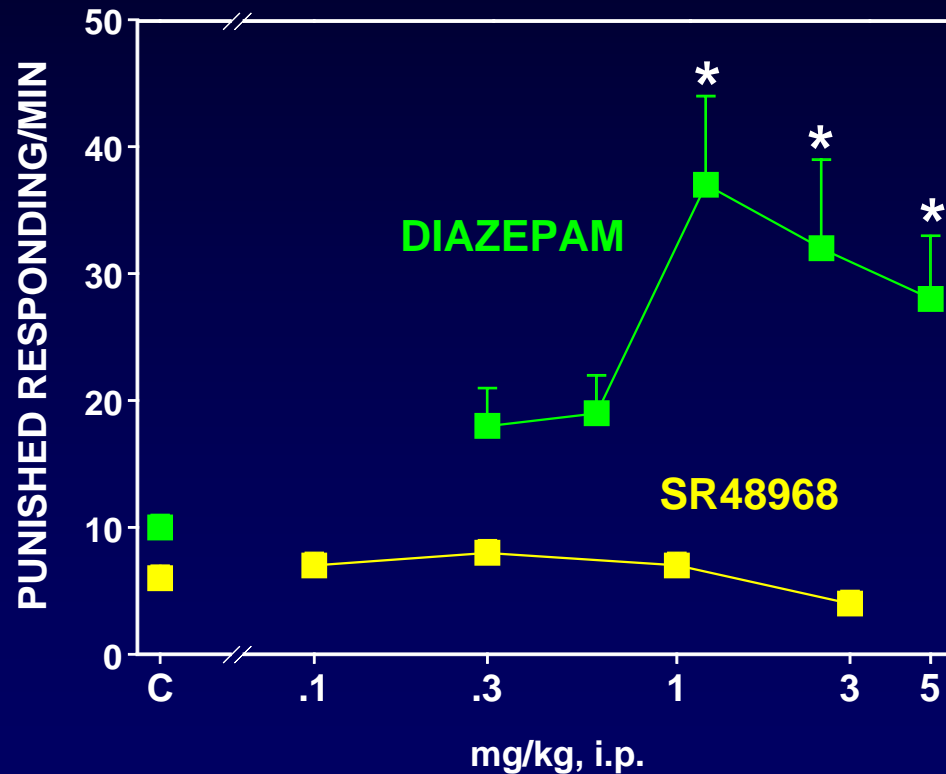
Major Depressive Disorder

Do NK₂ receptor antagonists have
anxiolytic-like properties ?

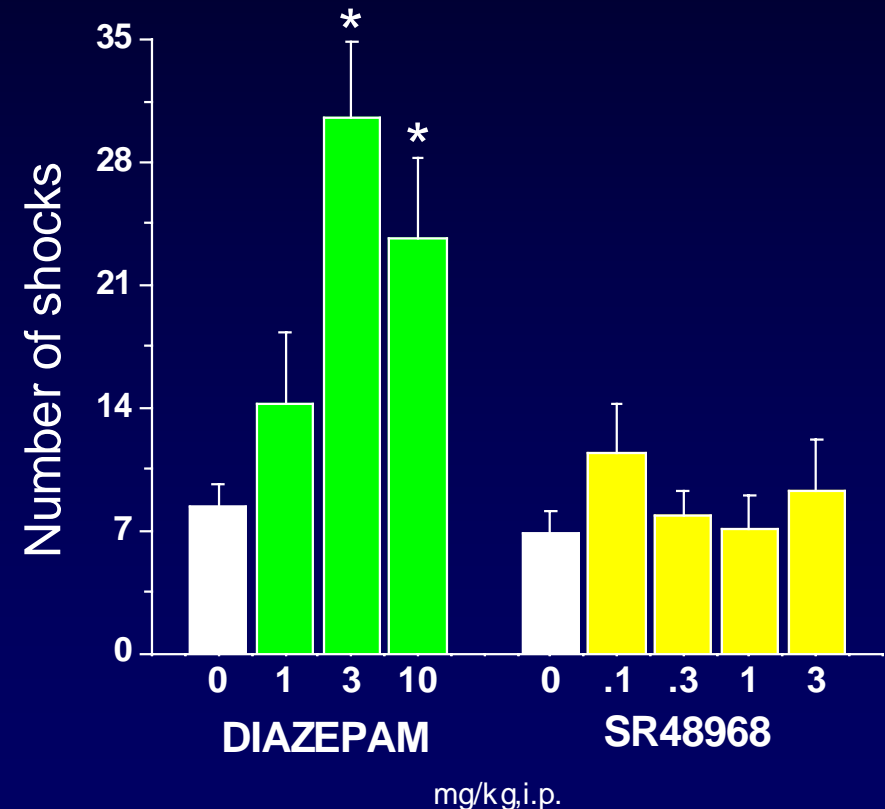
Evidence from behavioral and
neurochemical models of
anxiety/stress disorders

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

Punished lever pressing test

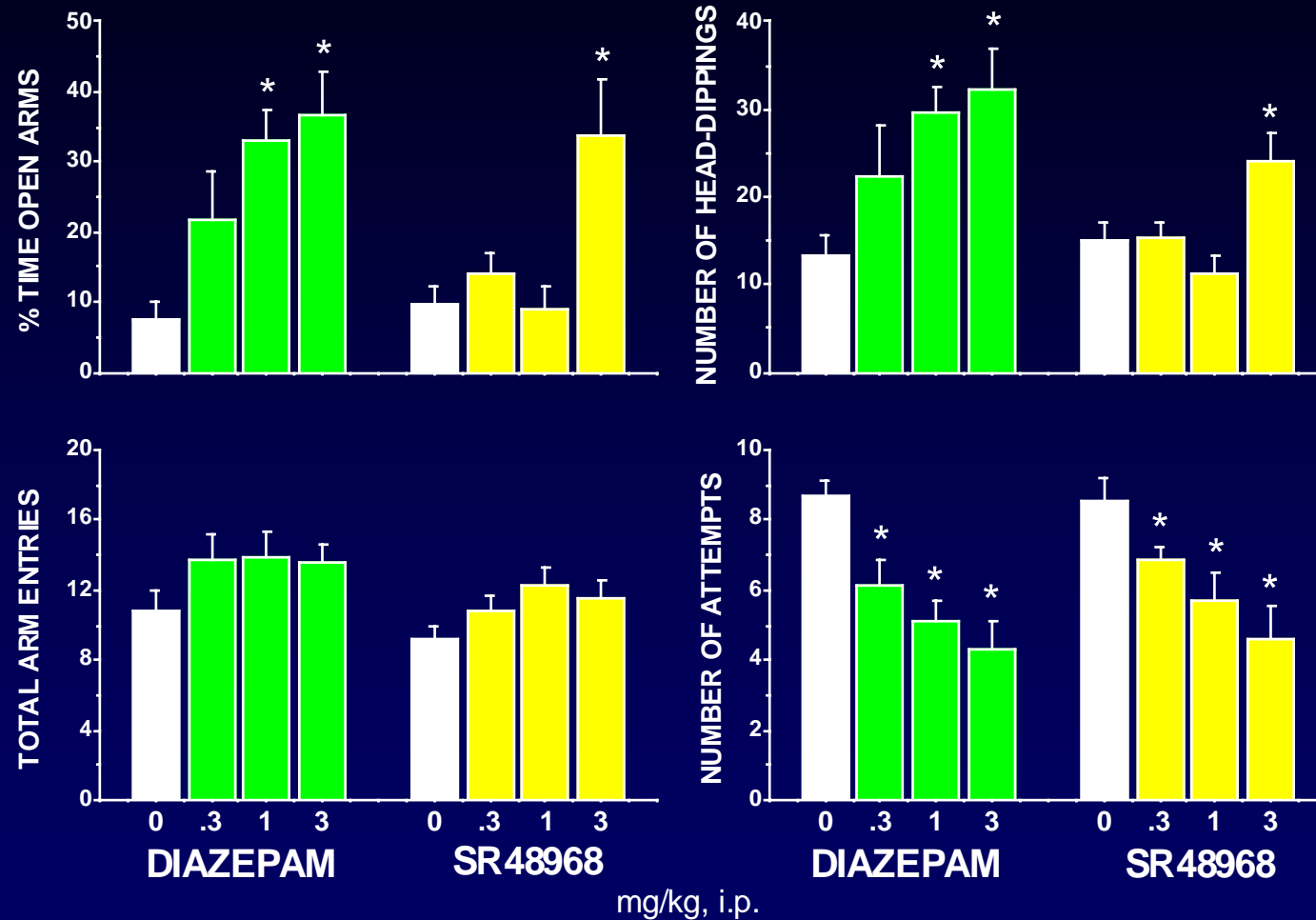


Punished drinking test



Griebel et al., *Psychopharmacology* (in press)

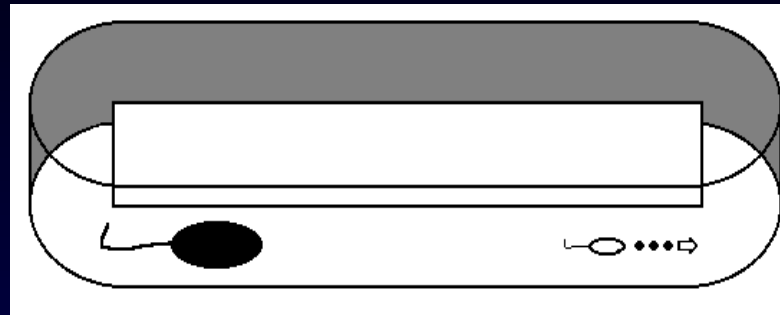
Effects of a selective NK₂ receptor antagonist in the elevated plus-maze test in rats



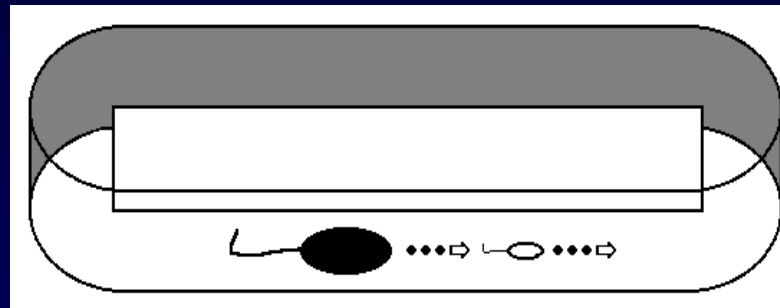
Griebel et al., *Psychopharmacology* (in press)

The mouse defense test battery

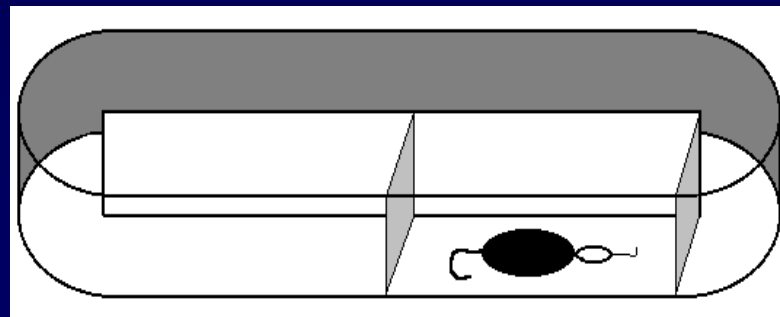
FLIGHT



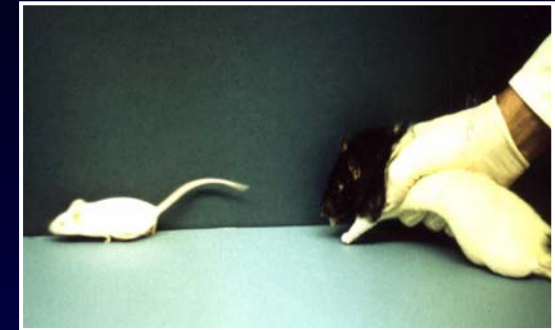
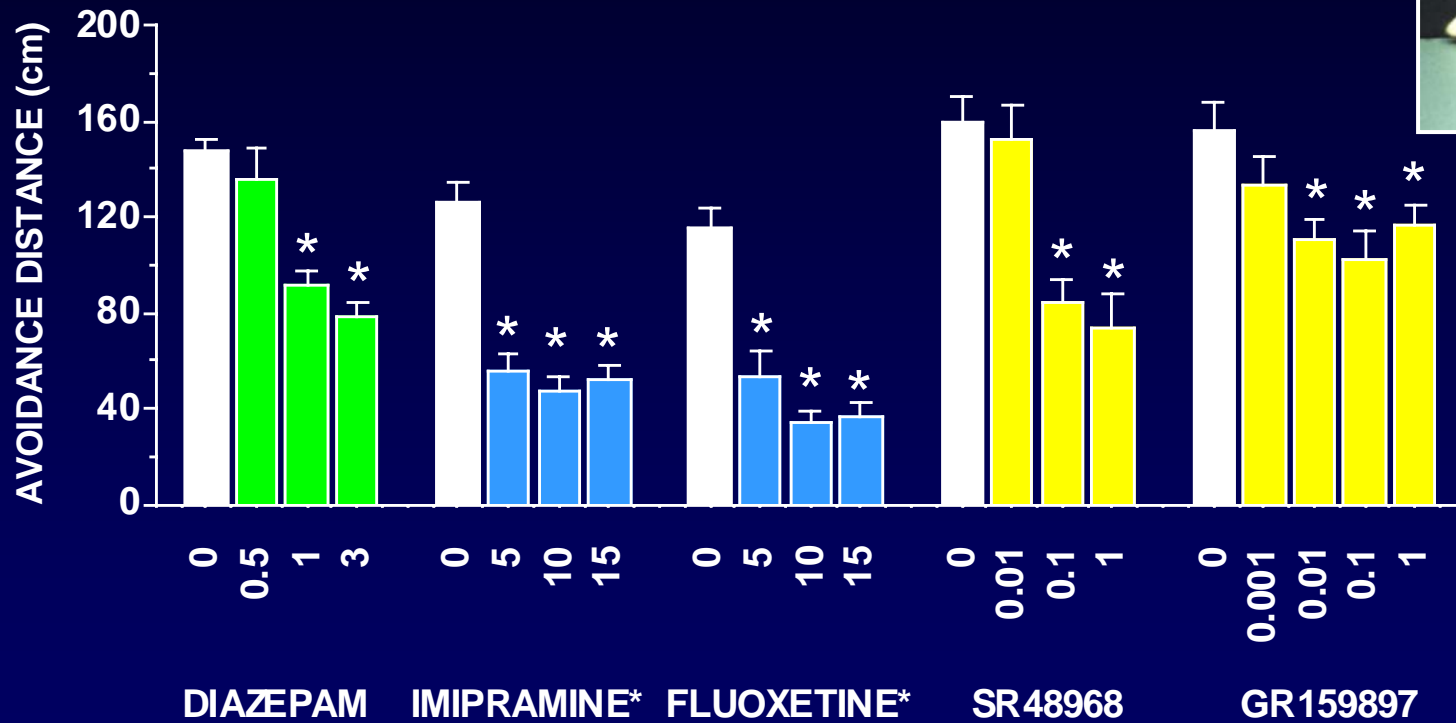
**RISK
ASSESSMENT**



**DEFENSIVE
AGGRESSION**



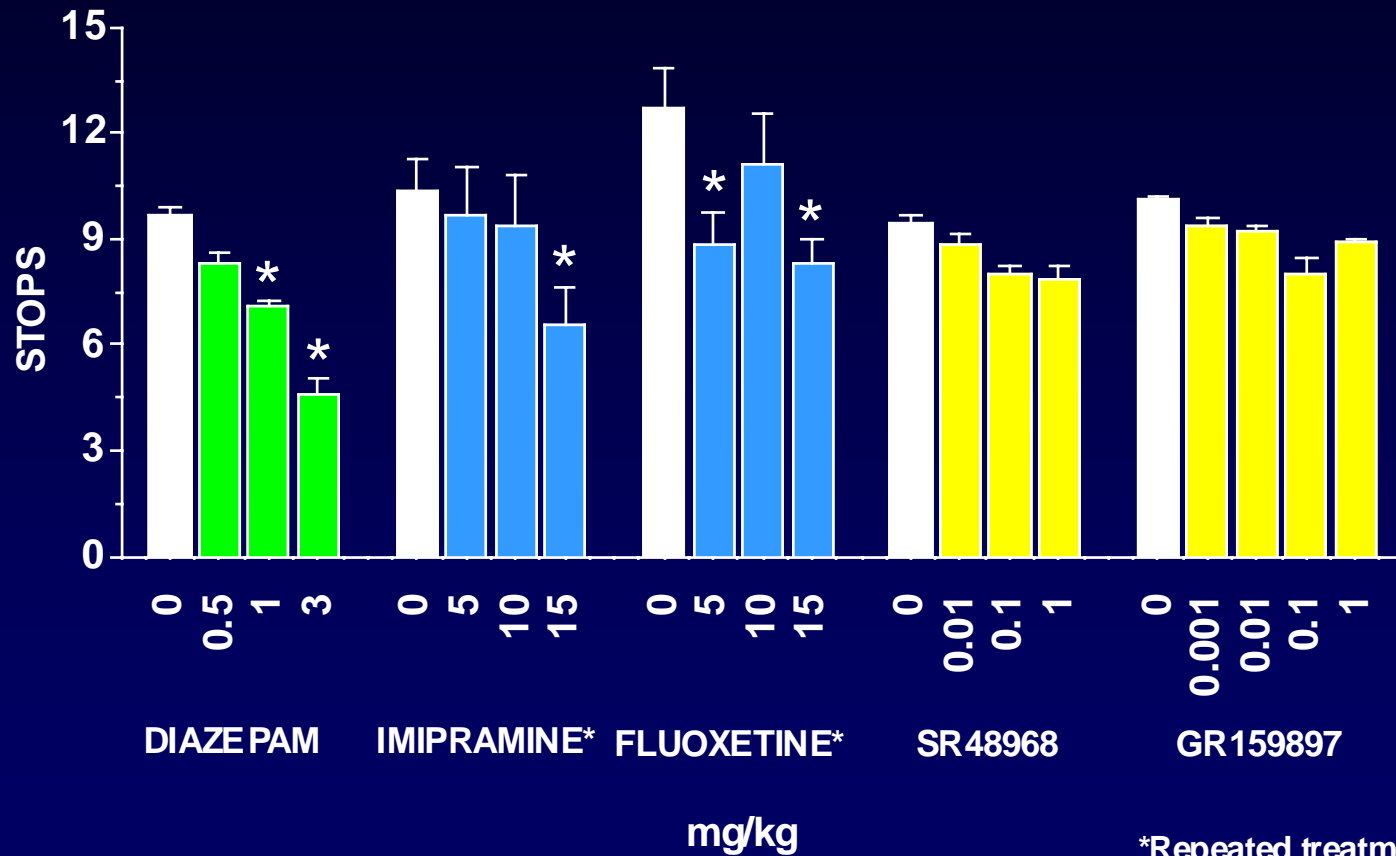
Effects of selective NK₂ receptor antagonists on flight behavior in the mouse defense test battery



mg/kg

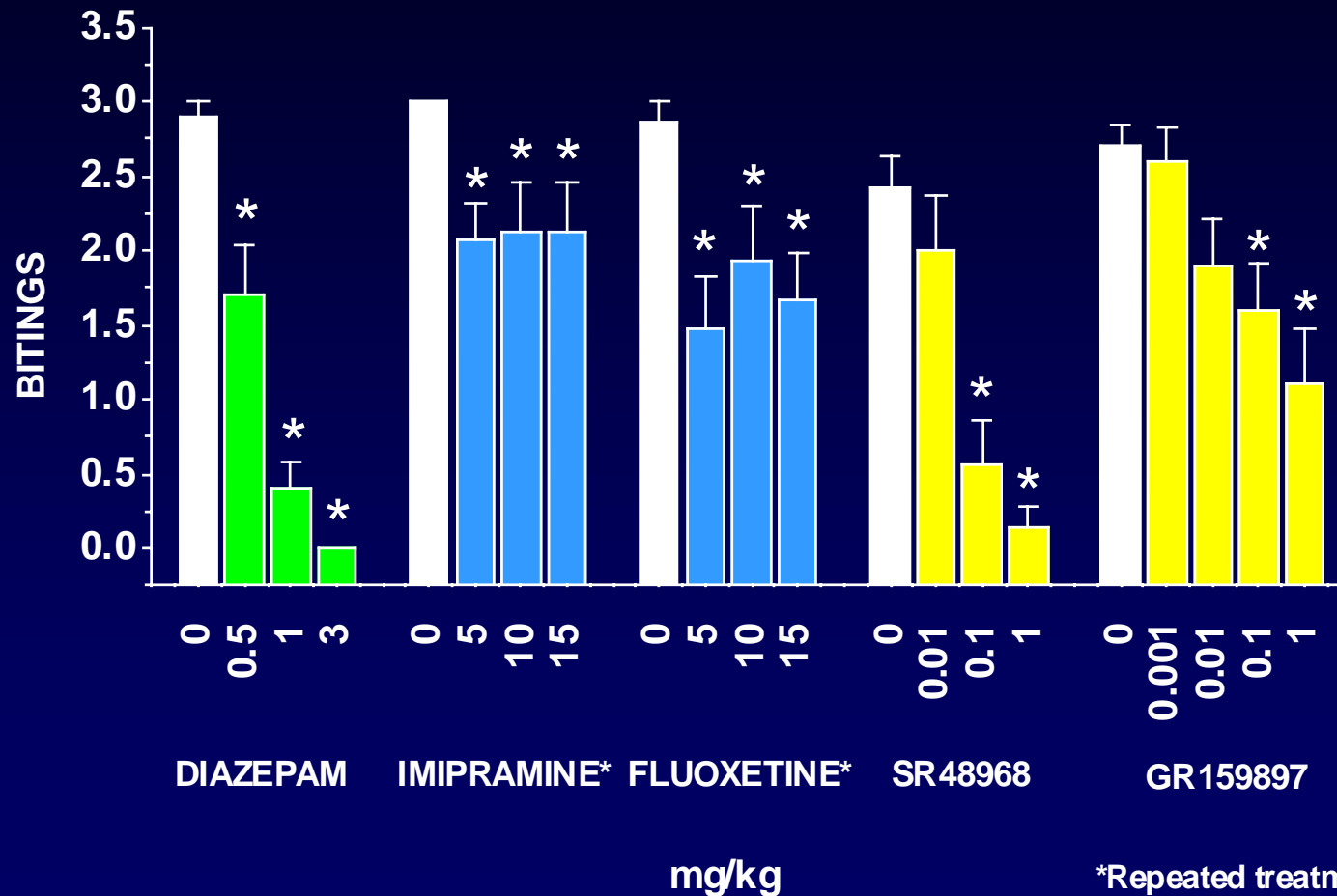
*Repeated treatment

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

Investigation of
the behavior of
rodents
following cat
exposure



Cat exposure (5-10 min)

60 min

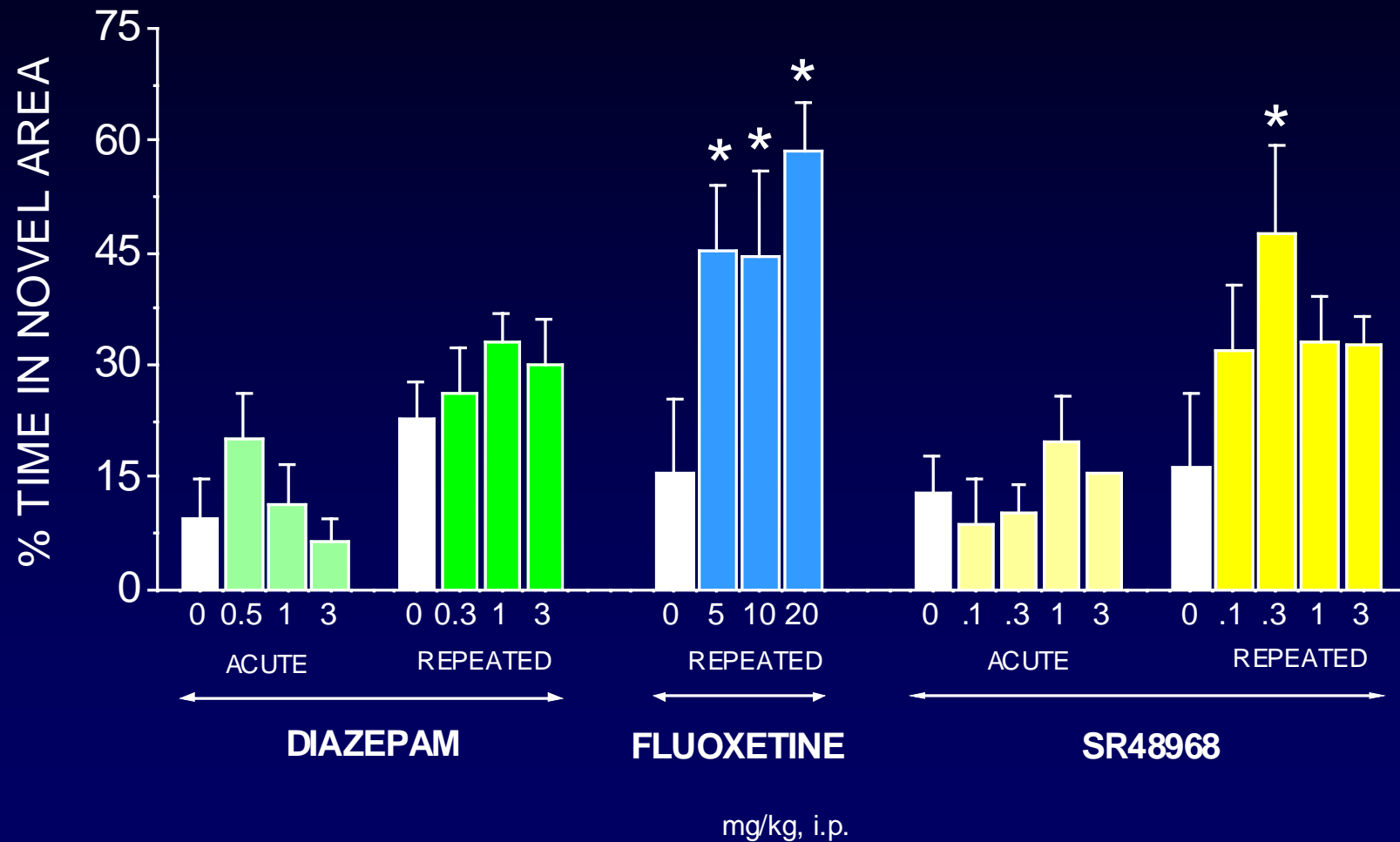


Free exploration test



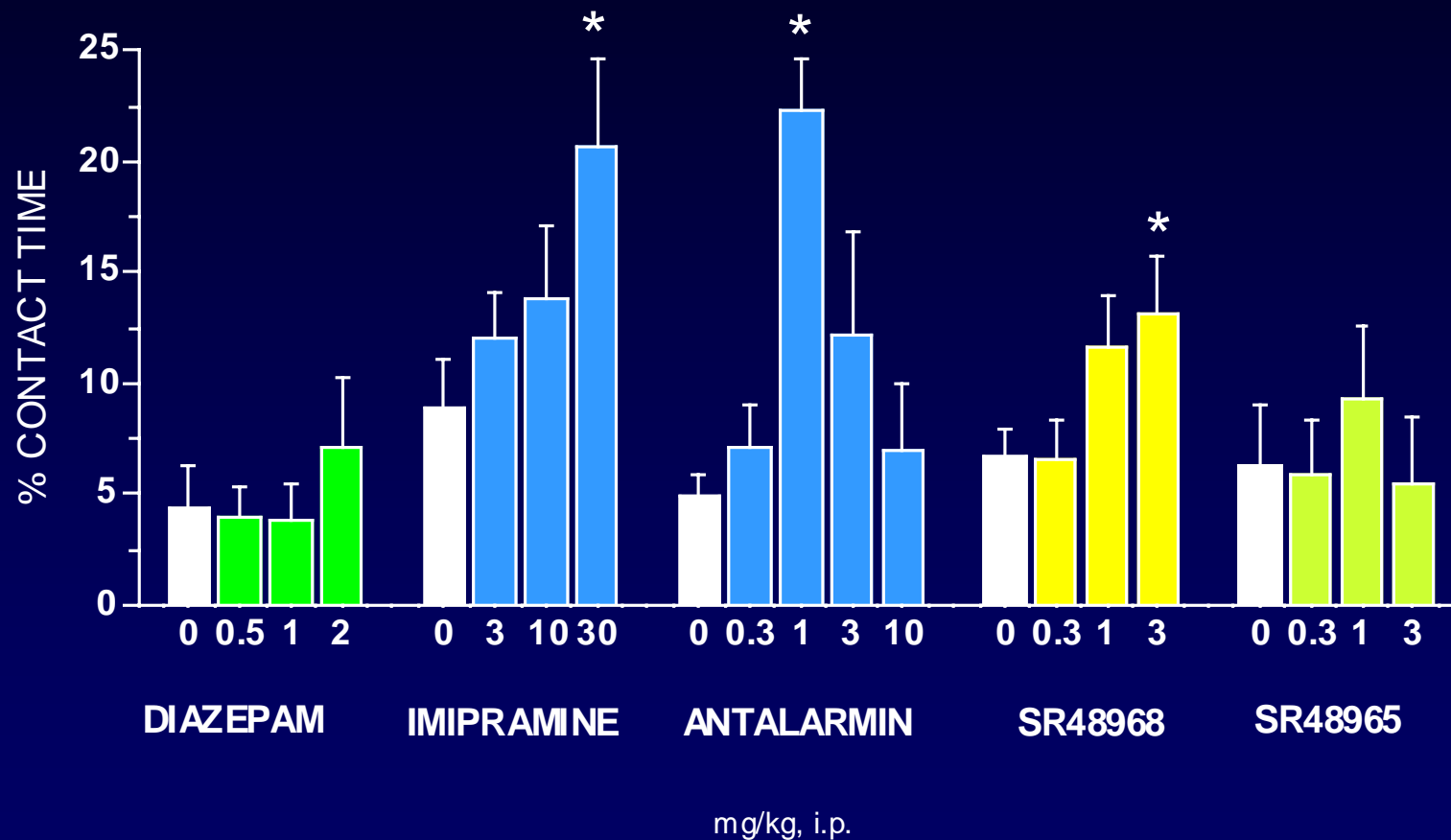
Staircase
test

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



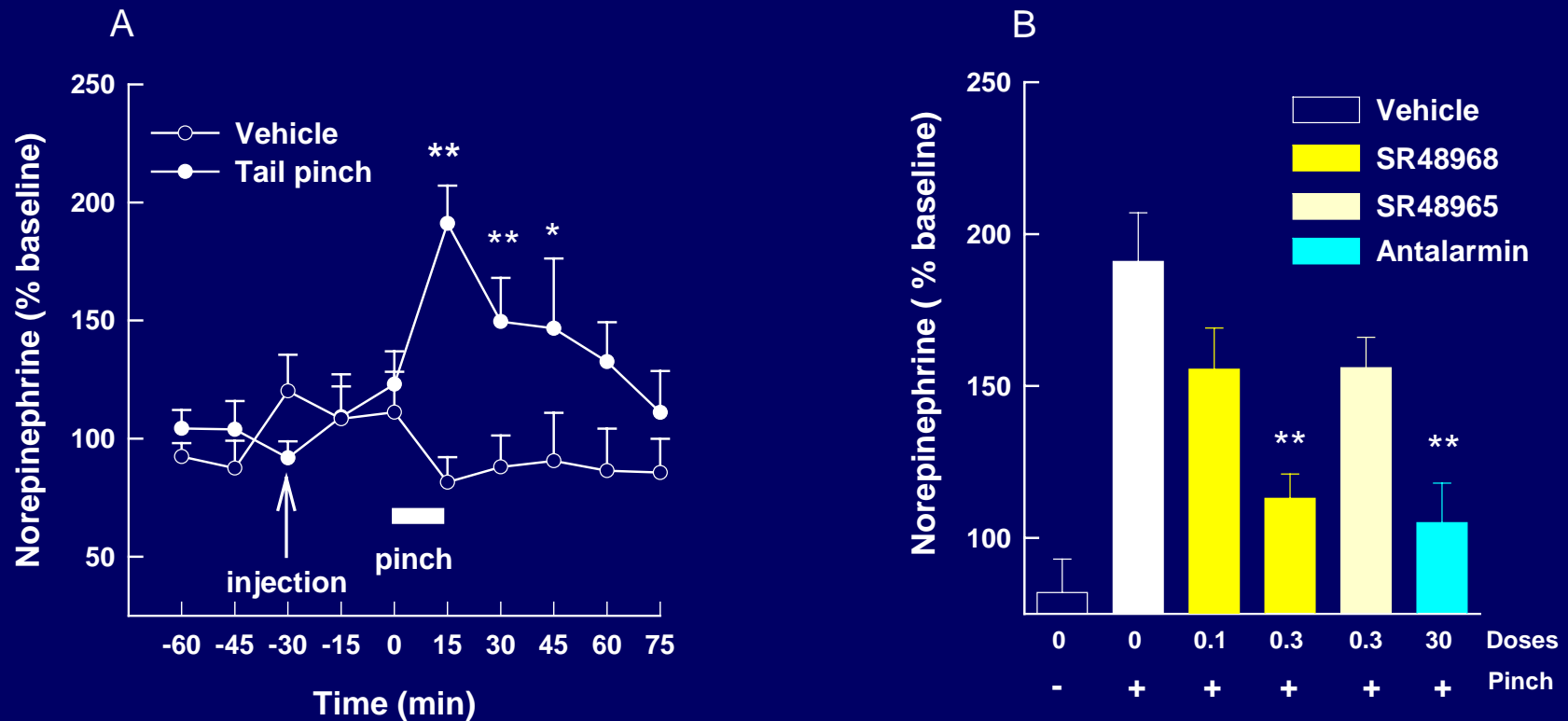
Griebel et al., Psychopharmacology (in press)

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



Griebel et al., *Psychopharmacology* (in press)

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



NK₂ antagonists in models of anxiety-related disorders

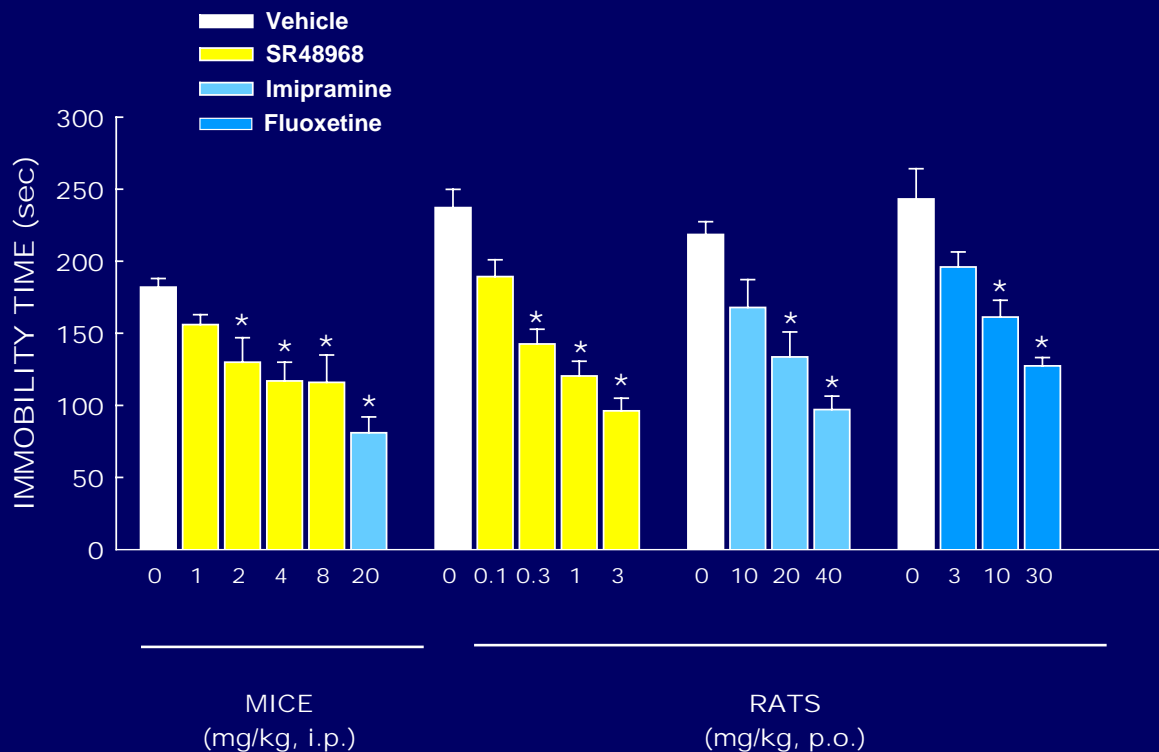
- ↙ **Show limited efficacy in models of anxiety sensitive to benzodiazepines**
- ↙ **Are active in situation involving unavoidable stressful stimuli or following traumatic stress exposure**

Do NK₂ receptor antagonists
have antidepressant-like
properties ?

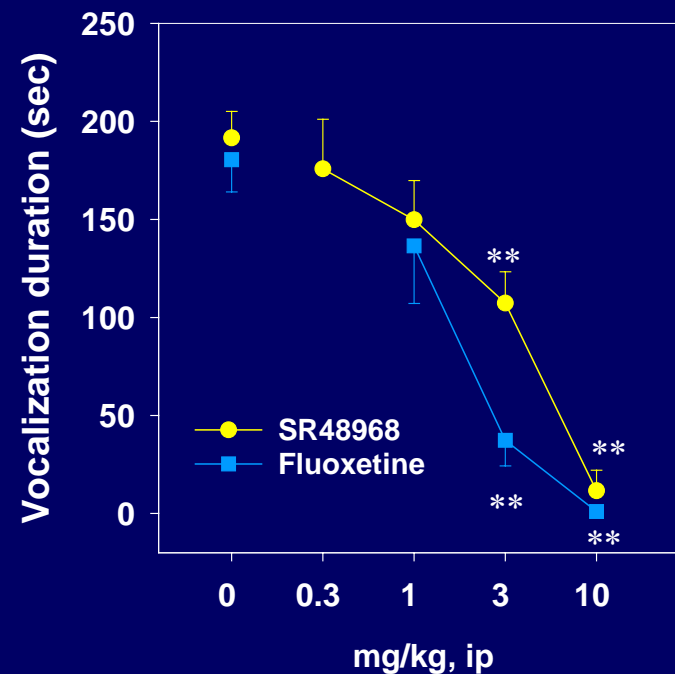
Evidence from behavioral and
neurochemical models of
depression in rodents

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

Forced-swimming test



Maternal separation-induced distress calls in guinea-pig pups



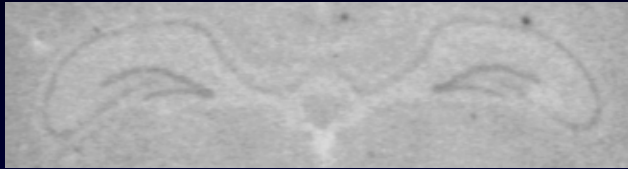
Steinberg et al., J. Pharmacol. Exp. Ther 299, 2001 (in press)

Antidepressants and CREB expression

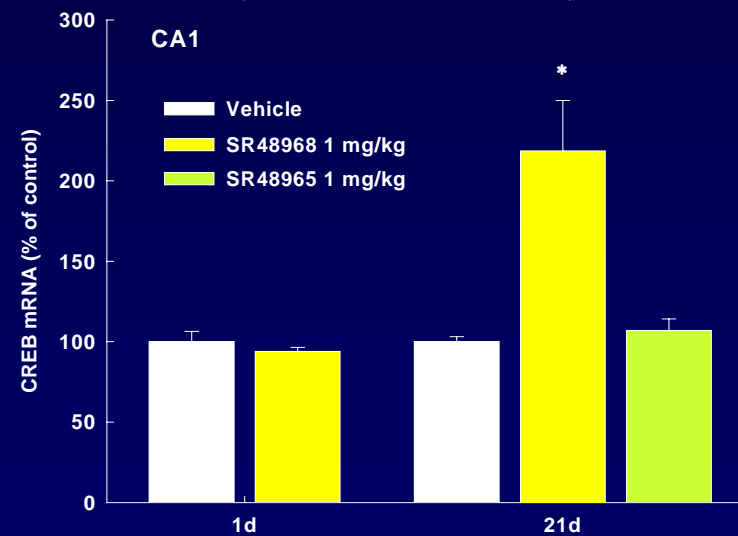
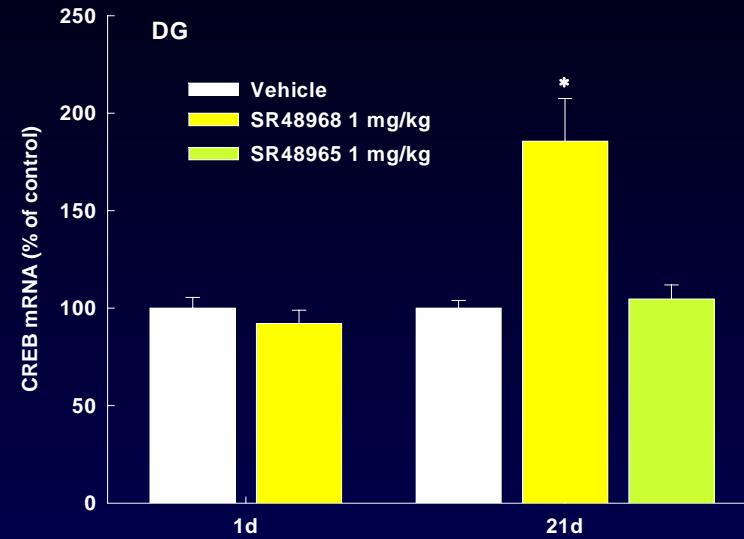
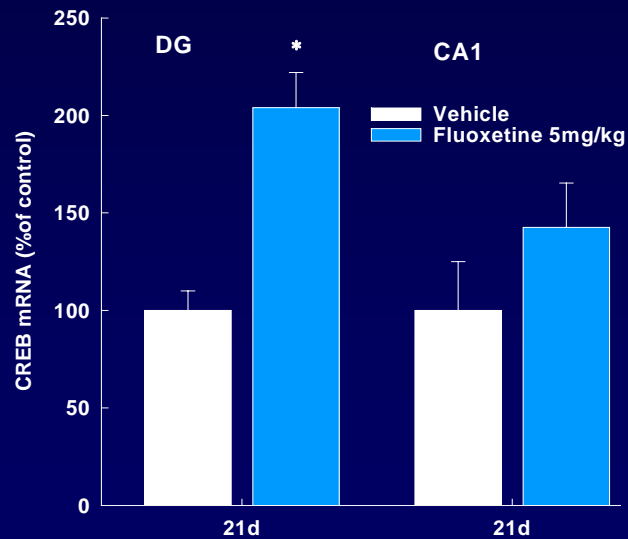
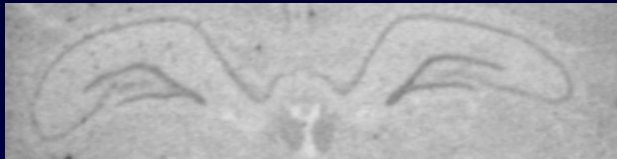
- ↙ **Studies in rodents have implicated the postreceptor components of the cAMP second messenger cascade in the action of different classes of antidepressants**
- ↙ **Chronic treatment with these drugs upregulated the cAMP system at several levels, including expression of the cAMP response-element binding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

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

vehicle



SR48968



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

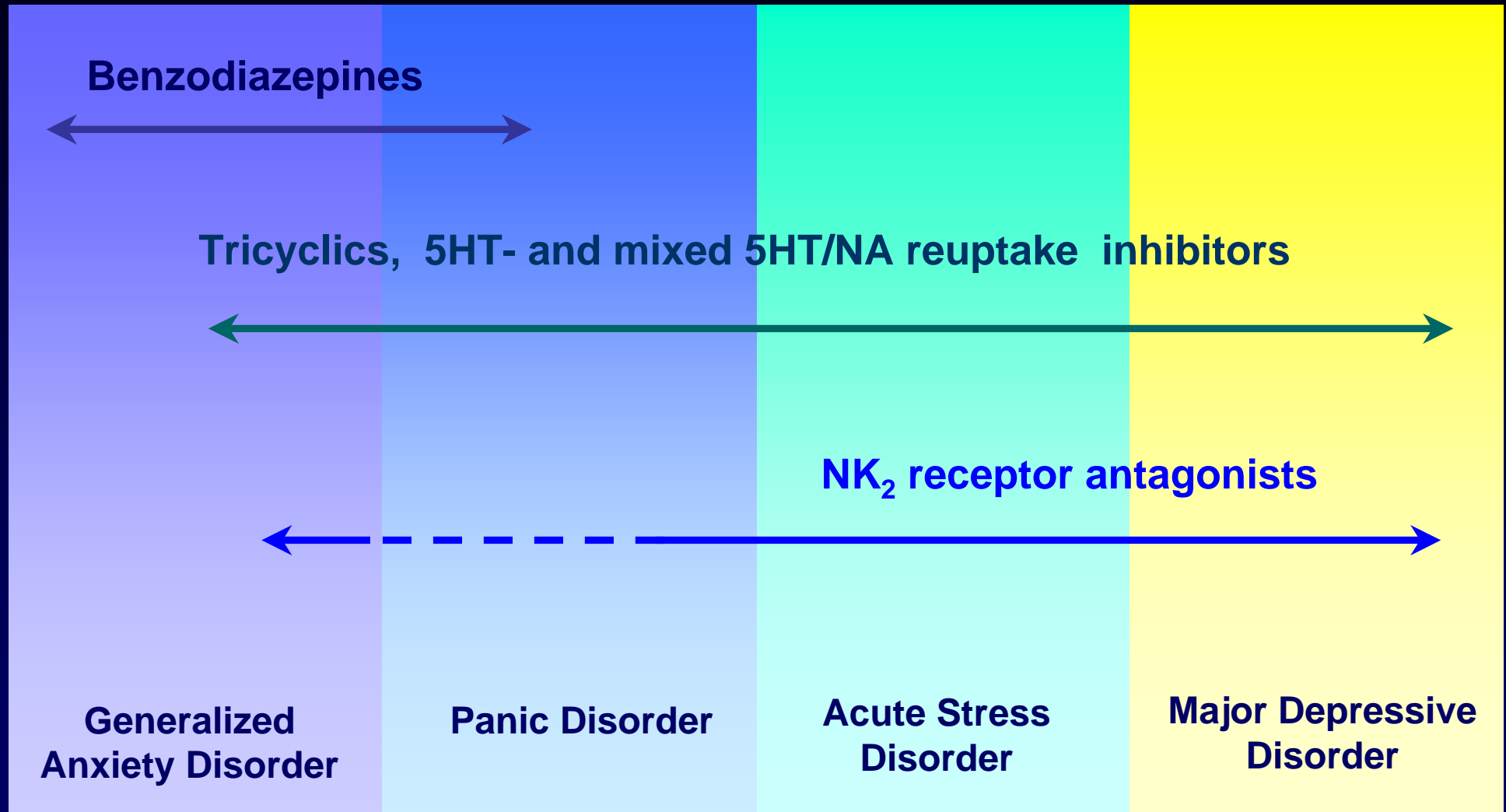
SR48968 in models of depression

- ↙ Shows good activity in two behavioral models
- ↙ Sustained blockade of NK₂ 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 NK₂ antagonists**
- ↙ **Unlike benzodiazepines, NK₂ antagonists were active in situations involving traumatic stress or unavoidable contact with threatening 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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- **Chemistry**

Emonds-Alt X.
Proietto V.
Van Broeck D.

- **Electrophysiological studies**

Gueudet C.

- **Anatomical studies**

Alonso R.
Jung M.

- **Neurochemical studies**

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