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

<table>
<thead>
<tr>
<th>Compound</th>
<th>hNK₂-CHO\text{pKi}</th>
<th>pA₂</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR159897</td>
<td>9.5</td>
<td>8.72</td>
<td>Beresford et al. (1995)</td>
</tr>
<tr>
<td>SR48968</td>
<td>9.9</td>
<td>10.3</td>
<td>Emonds-Alt et al. (1992)</td>
</tr>
<tr>
<td>SR144190</td>
<td>10.1</td>
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<td>Emonds-Alt et al. (1997)</td>
</tr>
</tbody>
</table>
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 \( \text{NK}_2 \) receptor expression in various rat tissues including septum (SP), striatum (ST), whole brain (BR) and colon (CL)

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# Structures and properties of rat tachykinin receptors

<table>
<thead>
<tr>
<th></th>
<th>NK₁</th>
<th>NK₂</th>
<th>NK₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acid residues</td>
<td>407</td>
<td>452</td>
<td>390</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>46.364</td>
<td>51.104</td>
<td>43.851</td>
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<tr>
<td>Preferred endogenous peptide</td>
<td>Substance P</td>
<td>Neurokinin A</td>
<td>Neurokinin B</td>
</tr>
<tr>
<td>Core homology</td>
<td>66 % to NKA</td>
<td>55 % to NKB</td>
<td></td>
</tr>
<tr>
<td>2nd messenger</td>
<td>IP₃-Ca²⁺</td>
<td>IP₃-Ca²⁺</td>
<td>IP₃-Ca²⁺</td>
</tr>
<tr>
<td>Expression Sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Peripheral tissues</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
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 \( \text{NK}_2 \) 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 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

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

[Graph showing the effects of different compounds on avoidance distance (cm) with repeated treatment in mg/kg]

DIAZEPAM  IMIPRAMINE*  FLUOXETINE*  SR48968  GR159897

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
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 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 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 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\textsubscript{2} antagonists

✔ Unlike benzodiazepines, NK\textsubscript{2} antagonists were active in situations involving traumatic stress or unavoidable contact with threatening stimuli

✔ The NK\textsubscript{2} antagonist SR48968 showed clear antidepressant-like activity
Expected clinical spectrum of therapeutic activity of NK₂ antagonists in anxiety/depressive disorders

- Benzodiazepines
- Tricyclics, 5HT- and mixed 5HT/NA reuptake inhibitors
- NK₂ receptor antagonists

Disorders:
- Generalized Anxiety Disorder
- Panic Disorder
- Acute Stress Disorder
- Major Depressive Disorder
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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 I.
  - Desvignes C.
  - Bougault I.
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  - Mons G.
  - Rodier D.
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  - Steinberg R.